EPIDEMIOLOGY AND ASSESSMENT OF PSYCHIATRIC DISORDERS IN EPILEPSY

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Thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy

2004

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ABSTRACT

This thesis addresses two important research questions. First, are common mental disorders commoner in epilepsy? Second, what are the instruments of psychiatric research that may be employed to assess psychiatric disorders in epilepsy? Two studies were conducted as part of this thesis: the first a primary care-based case-control study, and second, a study among institutionalised patients with epilepsy. Both studies used several psychiatric measures, and compared them with two gold standards: ICD-10 Criteria and "clinical significance" ratings.

Common mental disorders were significantly commoner in the epilepsy group than among controls. The instruments tested demonstrated good sensitivity and specificity, and we present revised cut-off scores for epilepsy populations. Psychiatric symptoms specific to epilepsy were good predictors of psychiatric caseness. The psychiatric measures used appeared to correlate better with clinical significance ratings than with ICD-10 criteria. Psychiatric co-morbidity rather than seizure severity had a significant impact on subjective handicap.

The institutional study revealed high rates of psychiatric co-morbidity, significantly more in patients with cognitive impairment. While different measures were correlated for overall psychiatric caseness, individual symptom categories were poorly correlated. An exploratory factor analysis of the NPI yielded a reliable and interpretable four-factor solution indicating good content validity. However, no

measure appeared to perform well, against either "clinical significance" or ICD-10 ratings, indicating poor concurrent validity.

These studies show that psychiatric co-morbidity is over-represented in epilepsy, and that it has a significant impact on disablement. Symptom-based measures of psychological burden may be more sensitive than conventional criteria in identifying psychiatric disorders in epilepsy. Both these studies favour the "clinical significance" approach in assessing patients with epilepsy. The burden of epilepsy specific psychiatric co-morbidity must also be explored systematically in future studies. The results from these studies underline the need for public health planners to address mental health issues in epilepsy.

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LIST OF ABBREVIATIONS

Abbreviation	Expansion
AD	Autistic Disorder
AEDs	Anti-Epileptic Drugs
ALC	Autistic Like Condition
ANOVA	Analysis of Variance
APA	American Psychiatric Association
BDI	Beck Depression Inventory
BPRS	Brief Psychiatry Rating Scale
CBT	Cognitive Behaviour Therapy
CI	Confidence Interval
CIDI	Composite International Diagnostic Interview
CIS-R	Clinical Interview Schedule – Revised
CMD	Common Mental Disorders
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CSAG	Clinical Standards Advisory Graph
CT	Cognitive Therapy
DIS	Diagnostic Interview Schedule
DSM-III	Diagnostic and Statistical Manual for Psychiatric Disorders, III Edition
DSM-IV	Diagnostic and Statistical Manual for Psychiatric

	Disorders, IV Edition
ECA	Epidemiologic Catchment Area
ECT	Electroconvulsive Therapy
EEG	Electroencephalogram
ESES	Electrical Status Epilepticus in Sleep
FSQ	Functional Status Questionnaire
GAD	Generalised Anxiety Disorder
GHQ	General Health Questionnaire
GLM	General Linear Model
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HARS	Hamilton Anxiety Rating Scale
HDRS	Hamilton Depression Rating Scale
ICD-10	International Classification of Diseases – 10th Edition
IDD	Inter-ictal Dysphoric Disorder
ILAE	International League Against Epilepsy
IPT	Interpersonal Therapy
IQ	Intelligence Quotient
LD	Learning Disability
MAOI	Monoamine Oxidase Inhibitors
MMPI	Minnesota Multiphasic Personality Inventory
NBI	Neurobehavioral Inventory
NBI-C	Neurobehavioral Inventory – Carer version
NBI-P	Neurobehavioral Inventory – Patient version

NCS	National Co-morbidity Survey
NEAD	Non-Epileptic Attack Disorder
NHS3	National Hospital Seizure Severity Scale
NIMH	National Institutes of Mental Health
NPI	Neuropsychiatric Inventory
NSE	National Society for Epilepsy
OCD	Obsessive Compulsive Disorder
PAS-ADD	Psychiatric Assessment Schedule for Adults with Developmental Disability
PCA	Principal Components Analysis
PD	Panic Disorder
PSE	Present State Examination
PSQ	Psychosis Symptom Questionnaire
QOL	Quality of Life
RA	Research Assistant
RCT	Randomised Controlled Trial
ROC	Receiver Operating Characteristics
SADS	Schedule for Affective Disorders and Schizophrenia
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
SCID	Structured Clinical Interview for DSM
SCID-E	Structured Clinical Interview for DSM-Epilepsy Version
SHE	Subjective Handicap in Epilepsy
SMR	Standardised Mortality Ratios
SNRI	Selective Norepinephrine Reuptake Inhibitors

SP	Social Phobia
SSRI	Selective Serotonergic Reuptake Inhibitors
SUDEP	Sudden Unexpected Death in Epilepsy
TCA	Tricyclic Antidepressant
TLE	Temporal Lobe Epilepsy
TMS	Transcranial Magnetic Stimulation
UK	United Kingdom
USA	United States of America
VNS	Vagal Nerve Stimulation
WHO	World Health Organization

ACKNOWLEDGEMENTS

The subjects in primary care and the residents of the National Society for Epilepsy who took part so enthusiastically

My supervisor Prof. Michael Trimble (Institute of Neurology, UCL), for his sustained academic mentorship, support, generosity, encouragement and continual guidance, without which these studies would not have been possible

My co-supervisor Prof. Martin Prince, for his friendship, sustained research mentorship, and for the many hours of epidemiological and statistical discussions over the years

My research assistants Dr. Lavanya Vijayaraghavan and Mr. Ravi Samuel for their enthusiasm, perseverance and diligence in collecting some of the research data

Dr. Redhead (King's Lynn), Dr. Hakin (Bradford), and their teams, for sharing their patients, and for their interest in this study

Dr. Richard Brown for early inputs into statistical methods; Dr. M. O'Donoghue for training the RA's in the use of the NHS3 and SHE and allowing us access to the primary care database

Principals and staff of the participating GP surgeries named herein

Prof. John Duncan, Director of the National Society for Epilepsy- Centre for Epilepsy, for commissioning and approving the audit/review of neuropsychiatric co-morbidity, and the institutional study thereof

The staff of the NSE Centre for Epilepsy for helping us in conducting the audit/ review of psychiatric co-morbidity

Professors Simon Shorvon and Ley Sander for their inputs

Funding agencies which supported these studies

Paul Hamlyn Foundation, London

Raymond Way Fund, Institute of Neurology

NSE Centre for Epilepsy

Bradford Epilepsy Service

Lundbeck-UK

My parents for having inspired and encouraged me

My wife Gayathri for her understanding, support and conviction; for standing by me

and making many a sacrifice just so that this may be possible & our delightful son

Aditya who could never understand why dad was often many miles away

1. PSYCHIATRIC EPIDEMIOLOGY & COMMON MENTAL DISORDERS

1.1. Psychiatric Epidemiology: Historical Introduction & Overview

Psychiatric epidemiology is the study of the distribution of mental disorders in populations and of risk factors associated with their onset and course. Epidemiological methods provide the tools to conduct systematic research in aetiology and genetics and serve as the basis of outcome studies and clinical trials. Epidemiology can be considered as one of the scientific foundations of psychiatry (Tohen et al., 2000).

1.1.1. Studies in the USA

Studies done in the United States of America have been divided into first, second, and third generation studies (Dohrenwend, 1995). The first generation studies were conducted at the end of the nineteenth and through the first half of the twentieth century. Early examples of path-breaking studies done in this period include that done in the 1920's by Goldberger (Terris, 1964) examining the role of nutritional deficiencies in the development of psychosis due to Pellagra. The second-generation studies followed World War II, as in this period, psychiatric illness was the leading cause for men being rejected from military service, and perhaps more importantly a major cause of discharge from the services and occupancy of half the hospital beds in the USA. The main improvement in the second-generation studies was that subjects were directly interviewed. Further, this period witnessed clinical and reliability studies, and the use of the 1st edition of the DSM (DSM-I) (APA, 1952) for classification.

1.1.1.1. Subsequent Developments in Psychiatric Epidemiology

The US/UK diagnostic project (Cooper et al., 1972) clearly illustrated the need to use standardised diagnostic instruments in psychiatric epidemiology. The development of the Feighner criteria (Feighner et al, 1972) and the accompanying Renard Diagnostic Interview Schedule (Helzer et al., 1981), and the development of Research Diagnostic Criteria (Katz et al., 1979) followed.

1.1.1.2. The Epidemiologic Catchment Area (ECA) Study

The ECA study was a landmark third generation study conducted in the U.S.A. Sponsored by the National Institutes of Mental Health (NIMH), this was a large population-based study to determine the prevalence of mental disorders and the amount and type of mental health services provided for those in need (Regier & Kaelber, 1995). One of the core features of the ECA was its use of the Diagnostic Interview Schedule (DIS) and DSM-III criteria for diagnosis.

Five sites were selected through a peer-reviewed process from all applications received in response to the NIMH solicitation. The ECA Study estimated lifetime prevalence, 1-month prevalence, and 6-month prevalence. It also estimated new cases during a 1-year period (1-year cumulative incidence) and the services received during that time by the populations under study. The lifetime prevalence of any disorder in the DIS was 32.2%. Substance use disorder at 16.4% showed the highest prevalence followed by anxiety disorder at 14.6%. Anxiety disorders and affective disorders together formed the greatest proportion of all psychiatric co-morbidity.

The ECA study also demonstrated a treatment gap for mental disorder, with only 28.5% of people with a DIS mental disorder having had a mental health visit in the past year, and only 60–70% of people with significant mental disorders (schizophrenia, bipolar disorder, somatization disorder and panic disorder) obtaining care.

1.1.1.3. The National Co-morbidity Survey (NCS)

Built on the experience of the ECA study, the NCS was designed to estimate the prevalence and co-morbidity of mental and substance use disorders in a representative sample from the continental United States (Kessler et al., 1994). The NCS focussed on individuals aged 15–54 years, used a stratified probability sampling procedure and included only non-institutionalised persons. Researchers sampled individuals in all 48 contiguous states for a total of 8098 subjects, 82.6% of the target population.

A modified version of the Composite International Diagnostic Interview (CIDI) known as the University of Michigan CIDI (Kessler et al., 1998) was utilised. The lifetime prevalence of any NCS disorder was 48.7% and the 1-year prevalence was 29.5%. As in the ECA survey reviewed earlier depressive and anxiety disorders formed a substantial proportion of psychiatric morbidity both in the lifetime and 1-year periods. In contrast, non-affective psychosis and mania formed only a small proportion of the overall figure.

1.1.2. International Studies

While the developing world has not gone un-represented, studies being conducted in countries like India, Brazil, and Kenya, the proportion of research involving the developing world has been limited. An important international study that bridged this knowledge gap is described briefly herein, as it addressed many issues pertinent to common mental disorders the study of which forms an important component of this thesis.

1.1.2.1. WHO Collaborative Study on Psychological Problems in Health Care

The WHO established this study as prospective, cross-cultural, epidemiological investigation to answer several important research and care related issues with respect to mental health in the developing world (Ustun & Sartorius, 1995). The study had a wide choice of sociocultural settings in which, no previous studies had taken place.

The study population consisted of consecutive patients attending the participating general health care facilities. Patients between the ages of 18 and 65 were included and screened using the General Health Questionnaire-12 item version (GHQ-12). As there were differences between centres both in terms of patient turnover and in terms of GHQ scores in the pilot project, centre-specific procedures for screening patients, and centre specific norms for GHQ scoring were developed.

Phase II consisted of a standardised in-patient interview lasting about an hour. This comprised of a section on the patients presenting complaint; the pathway to their health care visit; the primary care version of the CIDI; information on physical and psychological co-morbidity; assessments of social disability; the GHQ-34, self rated health status, and for clinically trained interviewers; clinical diagnosis according to ICD-10 and DSM-III-R criteria. The phase II subjects were followed-up at three and twelve months. The GHQ-28 was used in the three-month follow-up and the CIDI in the twelve-month follow-up.

In order to compare, reliably, a host of variables across cultures, the multi-trait multi-method approach was adopted (Campbell and Fiske, 1959). The strategy was to measure the same characteristic by two or more different methods, and then assess the correlation of alternative measures of the same construct and consistency of results across measures.

Twenty-four percent of consecutive attenders had current mental disorders reaching ICD-10 criteria for well-defined disorders (depression, dysthymia, anxiety disorder, agoraphobia, panic, somatization disorder, neurasthenia, hypochondriasis, alcohol dependence and harmful use) over all the centres. A further 9% had clinically significant symptoms clustering in anxiety, depression and somatisation groups that did not meet ICD-10 criteria for a psychiatric disorder (sub-threshold disorders). 31% had two or more mental disorder symptoms. There were wide variations in prevalence across the centres on all the three different measures of case-identification (CIDI, GHQ and primary care physician), ranging from a high estimate of 52.5% in Santiago de Chile to a low of 7.3% in Shanghai. However, the rank ordering of the centres

across the three measures was comparable, thus indicating that there were true differences between the centres (Goldberg and Lecrubier, 1995).

The commonest ICD-10 diagnoses were current depression (10.4%), generalised anxiety disorder (7.9%), neurasthenia (5.4%) and harmful use of alcohol (3.3%). Agoraphobia (with and without panic), Panic disorder and Hypochondriasis formed the lower end of the spectrum (between 0.5 and 1.1%). There was a wide spread of prevalence rates for both the common disorders (depression and anxiety), and wide variation among centres, depression being commoner in some and anxiety in others. While age did not account for differences in prevalence, gender did, with the Odds Ratio for all centres being 1.89, females being twice as likely as males to suffer from depression. While factors such as physical health and parity had no impact on prevalence, education did, with those having had the most years of full-time education having lower rates than those who were educationally disadvantaged. This however may be consequent to educational level acting as a proxy to social advantage (Goldberg and Lecrubier, 1995).

1.1.3. Studies in the United Kingdom

1.1.3.1. British Psychiatric Morbidity Survey

With mounting evidence about the massive global burden of mental illness, the Department of Health in Great Britain outlined a greater understanding of mental disorders through research, and the development of appropriate strategies to reduce the burden of mental health among its key objectives. As part of the agenda to

improve information and understanding about mental illness, the Department of Health commissioned the Office of National Statistics to survey psychiatric morbidity of the country in collaboration with an advisory group of psychiatric epidemiologists (Jenkins et al., 1997a). The purpose was to give a national picture of the prevalence, severity and duration of mental health and their accompanying disability; associated risk factors; and the extent to which health and social care needs are met by services, this being the first national survey in any country to collect such information simultaneously.

Four separate surveys had been completed by 1998 (Jenkins, 1997b; 1998). They were, a private household survey using postcode address files of small users as the sampling frame; institutional survey selecting randomly from hospitals, residential homes, hostels and group homes; a supplementary sample of people with known psychosis (to obtain information about service use) drawn from general practitioners and country mental health teams in the same 200 postal sectors; and a survey of homeless people in temporary accommodation, night shelters, or day centre attendees.

All responders in the household survey were interviewed by trained interviewers using the Clinical Interview Schedule – Revised (Lewis et al., 1992) leading to ICD-10 diagnostic categories; a psychosis screening questionnaire specially developed for the survey (Bebbington and Nayani, 1995); questions about alcohol and drug misuse/dependence (using quality/frequency questions from national surveys); questions about stressful life events, social supports, social disability, activities of daily living, education and employment; questions about long standing medical illness and medication. Those subjects scoring 12 and over in the CIS-R were interviewed

using the SCAN and also were asked further detailed questions about use of health, social and voluntary care services, and informal care. The procedure in the institutional survey was identical except that proxy interviews were carried out for those who were unable to co-operate, and in the supplementary sample all were assessed using the SCAN. In night shelters and day centres, there was a perceived need for shortened questionnaires, and the 12 item General Health Questionnaire replaced the CIS-R, as did shortened versions of the questionnaires on other variables.

The household survey (Jenkins et al., 1997b) achieved a response rate of 80%. The overall period prevalence (one-week) of neurotic disorders among adults was 160 per 1000. Thus one in six adults' aged 16–64 had suffered from a neurotic disorder in the week prior to their assessment. The prevalence of neurotic disorders in women (195/1000) was higher than in men (123/1000) the odds ratio being 1.63. Marital status was strongly associated with neurotic disorder; rates were substantially higher in separated, divorced and widowed individuals of both sexes and among cohabiting women. Unemployed people were about twice as likely to suffer neurotic disorders compared with people in work; those living in urban settings are likely to suffer 1.5 times as much than the rural dwellers. Individuals with neuroses were twice as likely to have sought a general practitioner (GP) consultation in the last week. However, one quarter of those with a neurotic disorder had not sought any professional help.

One adult in 20 had experienced symptoms of alcohol dependence in the preceding year, and one in 40, dependence on drugs. Alcohol dependence was twice as common and drug dependence five times as common among those who were unemployed. The overall prevalence of psychosis in the household survey was 4 per

1000, with the prevalence among urban dwellers being twice that for those living in rural areas. Two-thirds were in touch with specialist services, while 18% had seen only their GP in the year prior to the interview. A further 18% said that they had never sought professional help. A very significant proportion of those with psychiatric disorder in the household survey, not only psychosis, but neurosis as well, experienced social disability.

In the institutional survey, 70% of those residents for whom diagnosis were obtained, suffered from a psychotic illness (schizophrenia, schizoaffective, delusional disorders); 8% from an affective psychoses, and 8% from a neurotic disorder. The distribution of disorders varied depending on the setting- schizophrenia and related disorders being more common in the hospital than in the residential setting (74% vs. 67%), and the converse being true for neurotic disorder (12% vs. 4%). Patients with psychotic disorders tended to stay in the institution for longer periods than those with neurotic disorders.

In the survey of the homeless, that tapped various sources, the prevalence of neurosis was 38% among hospital residents, 35% among those living in private sector leased accommodation, 60% among night shelter residents, 57% among the homeless sleeping rough and using day centres. The prevalence of psychosis was 8% among hospital residents, 2% among private sector leased accommodation residents, and was not estimated among those sleeping rough. The comparative figure for those living in households was 0.4%. The prevalence of alcohol dependence was 16% among hostel residents, 3% among those living in private sector leased accommodation, 44% among night shelter residents, and 50% among homeless people sleeping rough

(compared to 5% of people living in households). The prevalence of drug dependence was 6% in hostel residents (11% including cannabis dependence), 22% in night shelter residents (29% including cannabis), and 12% in those sleeping rough (24% including cannabis).

This study illustrates that psychiatric disorders are a significant public health problem in the UK and an important cause of considerable disablement and distress. The link with social and educational disadvantage and the treatment gap identified point to the need for social needs to be addressed along with health needs (Jenkins et al., 1997a,b; 1998).

1.1.4. Conclusions from this Section

In sum, these epidemiological studies have helped achieve significant progress in psychiatric research. Data from across the world has demonstrated quite clearly that psychiatric disorders especially common mental disorders, are widely prevalent, and constitute a significant burden on public health services and the community.

1.2. Common Mental Disorder

The vast majority of psychiatric disorders encountered in primary care are characterised by symptoms of anxiety, depression and other symptoms of "neurosis". They are referred to as minor or mild psychiatric disorders in contrast to the more "major" psychotic disorders, which are serious and cause significant disability, but tend to be much less common.

Goldberg and Huxley (1992) coined the term "common mental disorder" to describe these disorders "that are commonly encountered in community settings, and whose occurrence signals a breakdown in normal functioning". These "Common Mental Disorders" (referred to henceforth as CMD) are an important cause of morbidity worldwide (Ustun et al., 1995), may be associated with significant disability (Ormel & Costa E Silva, 1995), and in about half the cases may become chronic (Mann et al., 1981).

It is also noteworthy that mood disorders, an important component of CMD, are common in psychological autopsy studies of suicides. CMDs therefore cause not just morbidity and disablement, but are an important cause of mortality due to self-harm. This is important with regard to epilepsy as it is well recognised that Sudden Unexpected Deaths in Epilepsy (SUDEP) do occur, and that in a proportion of cases self-harm is the cause (Sander, 2002).

This thesis examines the prevalence of CMD in patients with epilepsy compared to population-based control subjects, and studies the role of CMD as a cause of disablement in epilepsy. CMDs are therefore reviewed in detail here.

1.2.1. Classification of Common Mental Disorders

The two major classificatory systems of psychiatric disorders are the ICD-10 of the World Health Organisation (WHO) (WHO, 1992a) and the Diagnostic and Statistical Manual- fourth edition (DSM-IV) of the American Psychiatric Association (APA, 1994). While the DSM-IV and its precursor DSM-III are widely used and indeed preferred in many research settings, the ICD is the more international of the classifications, arising from consultation among experts and research around the world. In ICD-10 CMD are classified mainly under two categories: "Neurotic, stress related and somatoform disorders (F40-48)" and "Mood (affective) disorders (F30-39)" with numerous sub-categories in each section. There however remain a number of conceptual and practical problems. There is considerable overlap between these categories. For example, the co-morbidity between depression and anxiety is high, and it is often difficult to decide which the primary illness is. Further, some problems included here such as Obsessive-Compulsive disorder or OCD (F42), are rare in community surveys, while others (e.g. Social Phobia- F40.1) may not be considered a disorder.

A primary care version of ICD-10 has been developed for use in general medical and primary care health settings. This was developed as classifications used by psychiatrists are generally found to be too complicated for use in general medical

settings and GPs are unlikely to use these classifications in their practice -(Jenkins et al., 1998). The primary care version is brief (containing a small number of categories), easy to understand, linked with advice on management (including treatment), compatible with the full version of the ICD-10 and other classifications, and is reliable (Ustun et al., 1995). The categories chosen for inclusion in this version the ICD-10 PHC are all reasonably common in primary care settings. The arrangement of the categories generally follows ICD-10 although some categories (example depression, anxiety, stress-related disorders and unexplained somatic symptoms) have been grouped together, reflecting the difficulties in making sharp distinctions in primary care settings. Field trials have been conducted in many centres (Ustun et al, 1995). The ICD-10 PHC has been found useful in both recognition and management of mental disorders in these settings, increasing the range of symptoms considered by primary care practitioners, and adding to the management of depressive illness including changes in prescribing practices (Goldberg & Lecrubier, 1995).

1.2.2. Defining a Case

Unlike physical disorders, psychiatric disorders do not have clear markers that lead to diagnosis and case finding. Clinicians and scientists have thus relied upon clinical symptoms and syndromes for diagnostic purposes, and over the years consensus has developed over certain broad classes of classification. In the past two or three decades, the growth and development of psychiatric epidemiology has led to a shift in focus from studies in institutional settings to those in the community, leading to discussion and debate about diagnosis in psychiatric epidemiology (Williams et al., 1980; Wing et al., 1981). Two important aspects related to diagnosis in

epidemiological surveys. case definition (the delineation of criteria for regarding an individual as suffering from disease) and case identification (the methods used to identify members of the study population who fulfil these criteria) are discussed here.

As psychiatric illness is not measurable in the same way as physical illness, the decision as to whether a given individual suffers from a psychiatric disorder is based on the opinion of psychiatrists, which is considered to be the gold standard. Such opinion is derived from clinical experience and applied either in a single stage (as the criterion for caseness) or in two stages with probable cases being identified by screening, which is then confirmed or eliminated in psychiatric inter view.

However, the concept of the clinically identified patient being used as the yardstick in epidemiology is itself controversial for several reasons. The clinical process is fundamentally different from the epidemiological process. In clinical practice the psychiatrist is presented with a problem and the decision he/she is faced with is about the nature of the problem. However, the epidemiologist in psychiatry has a more fundamental issue at hand- i.e., is there a problem here, or in other words is this given individual a case? Thus, in this setting, caseness is neither assumed nor implied, and precise measurement of cases and accurate definition are important. Following on from this basic difference, there are linked differences in definition and reliability between the settings. Diagnosis in clinical psychiatry is rather more intuitive and thus non-standardised. In contrast, operationalised criteria for diagnosis and standardised instruments of psychiatric research have greatly increased the reliability of diagnosis in research settings.

Thus, at first sight the concept of psychiatric caseness seems at best confusing and possibly even unhelpful (Prince, 1998). For example, the estimates of depression in later life, in one comprehensive review on the subject, varied from 2% to 13% based on the criteria used for diagnosis. This depended on whether the diagnostic criteria used in the concerned study were broad or narrow. Broad criteria are often based on a clinician's impression of "clinical significance" (of severity and/or causing distress/disablement), and narrow criteria such as DSM, focus on a small and ubiquitous group of subjects with severe psychiatric disorder.

Thus the correct question is usually not so much 'What is a case?' as 'A case for what?' (Prince, 1998). The narrow criteria for major depression define a small proportion of persons with an unarguably severe form of depressive disorder, implying strong construct validity. This may be eminently suitable when it comes to a randomised controlled trial (RCT) of a new treatment for depression, or indeed to identify a pure case for a genetic linkage study. However, these criteria will not suit all purposes, missing as they would the large proportion of subjects whom clinicians would typically diagnose and treat in the community. Further, although depressed persons are known to be heavy users of health and social services, cases of major depression account for a very small proportion of this excess, which is mainly made up of cases with "common mental disorder". Further, diagnostic criteria may be capricious, many persons meeting some but not all the requisite case criteria, and nevertheless experiencing a significant intensity of symptoms, and loss of quality of life (Prince, 1998).

1.2.2.1. Methodological Problems with Case Finding

Psychiatric research has for the past two decades been preoccupied with the first task of science, i.e., learning how to define and measure the phenomena with which it deals (Thompson, 1989). The situation is complex due to several factors:

- The absence of tests of diagnostic utility that can distinguish between different types of psychiatric disorder
- The inability to relate severity of the disorder to severity of psychiatric symptoms
- The limited transferability of psychiatric ratings between situations- i.e., between different groups of patients, different raters, different cultures, and in the same group at different times

The pragmatic researcher has to accept these limitations, by accepting the inadequacies of knowledge, and measuring as accurately as possible, under the circumstances (Thompson, 1989). A product of the standardisation of clinical practice and understanding in psychiatry, are rating scales.

1.2.2.1.1. Which Symptoms to Measure?

In general, few symptoms can be described as being characteristic of a mental disorder, even in the setting of the hospital. This becomes true in the community setting, with symptoms in this setting often being non-specific in nature. Case finding instruments are generally developed through a process of consultation among experts

who identify a pool of common symptoms characteristic of the given disorder. Some items that comprise such instruments are also included on the basis of their ability to discriminate between cases and non-cases. A third factor that may play a role in case identification is symptom patterns, a particular combination of symptoms having superior discriminatory power when compared to individual symptoms, highlighting the need to assess clinical and statistical relationships.

Therefore, there are two major difficulties to surmount before a tool could be devised, aimed at measuring psychiatric disorder. First, to define what is meant by the term, so that it does not become meaningless; and second, to show that there is some common factor among the now limited domain of psychiatric disorders (Goldberg & Williams, 1988). Generic screening tools such as the GHQ are based largely on hierarchical models of diagnosis, wherein the more differentiated symptoms often distract attention from, or override the lesser. Foulds and Bedford (1975) also provided evidence for supposing that most patients with psychiatric disorders are disturbed at the lowest level of their hierarchy, what they referred to as dysthymic disorders. "An individual falling into any of these states may be said to be disturbed, emotionally stirred up, and altered in this respect from his normal self. Such states are therefore common to almost all psychiatric patients, and hence as a class, have little or no discriminating power. They are more 'understandable' than the symptoms of the other classes, are perhaps more often related to prevailing circumstances and are experienced by most of us at some time and with some intensity". Goldberg and Williams (1988) noted that two additional features might be added to the aforementioned description – tendency to develop minor somatic symptoms, and changes in outwardly observable social behaviour.

1.2.2.1.2. How are Symptoms to be Measured?

Some instruments rely upon the number of symptoms, each symptom being of equivalent value; and the subjects with a greater number of symptoms (possibly of low severity) are more likely to be recognised than subjects with fewer symptoms of significant severity. A good early example of such an instrument is the Langner 22 item screening inventory (Langner, 1962). More traditionally however, the presence of a critical number of a particular constellation of symptoms experienced over a critical length of time has traditionally been employed to diagnose psychiatric disorder (Goldberg & Huxley, 1992).

It is therefore often of more interest to be able to examine a profile of scores rather than a single score. There are several scaled scoring tests to choose from, and most can be used as general case detectors by adding the scaled scores together. For example, the scaled General Health Questionnaire or GHQ-28 was derived by factor analysis, and consists of four sub-scales for somatic symptoms, anxiety and insomnia, social dysfunction and severe depression (Goldberg & Williams, 1988).

Counting the number of key symptoms that patients report on a standardised research interview, and expressing the result on a scale can also measure severity of disorder. The index of definition (ID) is such a scale derived from the Present State Examination and expresses a degree of certainty that a diagnosable mental disorder is present (Wing et al., 1978). Respondents with non-specific symptoms will score ID2 or 3; sub-threshold disorders score ID4; definitely diagnosable disorders at the

threshold score 1105; and scores above that represent an increasing severity of undoubted mental disorders. A similar system is used in Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (WHO, 1995).

The time-period over which symptoms are to be measured is also important. For example, Salkind (1976) described three patterns of anxiety, short lived symptoms due to stress, baseline sub-threshold symptoms exacerbated by stress that eventually resolve, and chronic symptoms. Here, the first group would be considered normal, exemplifying the importance of a minimum duration of symptoms for the diagnosis of psychiatric disorder. Transient mental symptoms related to stress are common and part of normal human experience; they should not be diagnosed as a disorder unless they meet minimal time criteria. Traditionally, this period is two weeks for depression (WHO, 1992a) and is used to exclude adjustment disorders due to stressful life events. The second group may have subjects predisposed to developing significant symptoms when exposed to stress, by virtue of premorbid state, personality and past experience. Indeed, a number of subjects with chronic or recurrent symptoms would fall in this group. The third group on the other hand may consist of subjects with personality disorders. It is noteworthy that many chronic and disabling states, generalised anxiety disorder and dysthymia, for example, require a time criterion of several weeks of active symptoms to be fulfilled, before such a diagnosis can be made.

Further, in the measurement of symptoms and its interpretation, the role of response bias needs to be considered. The common response styles that affect results include acquiescence set (tendency to agree or disagree with items irrespective of

their content), and social desirability set (tendency to agree with items considered by the respondent as socially desirable). While the former can be minimised by balancing questions that require positive and negative responses (half each), psychological disorders by their very nature are considered socially undesirable, and the latter bias may not be responsive to such measures.

1.2.2.1.3. Estimating the Validity of Such Measurement

The validity of an instrument is defined as "the degree to which it measures what it is designed to measure" (Marder, 1995). Several types of validity have been described here. Face validity describes the degree to which the scale appears to measure what it claims to measure; Content validity refers to whether the content of the instrument is appropriate to the variable being measured; Criterion oriented validity is demonstrated by comparing the instrument with generally agreed upon objective external criterion; Concurrent validity and predictive validity are two types of criterion-oriented validity. Concurrent validity is the demonstration of a correlation between scores and the external criterion, both measurements being made at the same time. Predictive validity is the demonstration that scores predict the later occurrence of the external criterion/particular outcome.

Scores on instruments like the GHQ can be interpreted in three ways – First, they can be regarded as a measure of the severity of the psychological disorder. No assumptions need to be made about where normality ends and caseness begins. The most appropriate approach to establish validity in this sense will be to compute a correlation co-efficient between the scores on the questionnaire and some measure of

the severity of psychiatric illness derived from the criterion interview. Second, they can be used to estimate the prevalence of psychiatric illness, using a procedure by which scores are adjusted by means of validity coefficients to obtain an unbiased estimate of the true prevalence. Third, they can be regarded as an indicator of morbidity: in this use, the proportion of subjects with high scores is regarded as an indicator of psychiatric disorder.

The decision as to what is to be held as a "high score" is usually determined by finding the best trade-off between two validity coefficients (Goldberg & Williams, 1988). The validity coefficients most commonly estimated and used are:

- Specificity -proportion of true normals correctly identified
- Sensitivity – proportion of true cases correctly identified
- Misclassification rate – proportion of respondents correctly identified
- Positive predictive value – proportion of high scorers who are cases
- Negative predictive value – proportion of low scorers who are not cases

However, these measures only provide information about the performance of a screening instrument at one cut-off point. They do not provide information about the discriminating ability of the instrument across the total spectrum of morbidity, neither do they assess for the effect of varying the threshold score, nor they permit accurate comparison of the two screening tests. These latter assessments can be easily accomplished by receiver (or relative) operating characteristic (ROC) analysis – a technique that is reviewed in detail herein (4.8.2, pg 178).

1.2.2.1.4. Understanding the Case Versus Non-case Concept

If psychiatric morbidity were considered to be distributed across a continuum, the concept of a case – non-case dichotomy would appear meaningless. However, distinguishing ill people from those who are not an important part not just of clinical care, but of epidemiological studies and of health care provision/planning as well. The cut-off points assigned to distinguish a case from a non-case, differ not just between instruments, but also within the same instrument at different points in time and when it is being used for different purposes. Misclassification of cases and non-cases is not uncommon, as the vast majority of these instruments measure probability as opposed to absolutes. However, depending on the purpose for which the given instrument is being used, the misclassification rate can be minimised, either by increasing the threshold score to improve specificity and lower sensitivity, or by decreasing the score to achieve the converse.

1.2.2.2. Recognition of Common Mental Disorders in Primary Care

The recognition of common mental disorders in the primary care setting is often rather more problematic than one would expect. Recognition rates vary, depending on the setting (personal vs. clinic centre) (Ustun & Von Korff, 1995); the physician (psychologically minded or not) (Goldberg & Huxley, 1992) and the instruments employed (clinical ratings, self-rating questionnaire, structured or semi-structured interviews, and so on). A number of papers have attempted to study the relative merits of different tools often with interesting results (Brugha et al., 2001).

The WHO study of psychological problems in primary care (Ustun & Sartorius, 1995), described in detail earlier in this section, examined the recognition rate of common mental disorders by primary care physicians. Three different techniques of case identification were employed:

(1) Cases with diagnosable psychiatric disorder using ICD-10 criteria, derived from the CIDI-PHC interview.

(2) A high score on the General Health Questionnaire (GHQ)- self-report by the patient.

(3) Cases identified by the clinician as currently suffering from a common mental disorder on clinical grounds.

Similar prevalence figures were identified using the CIDI (24%), GHQ (23.2%) and clinician ratings (23.4%) (Goldberg & Lecrubier, 1995). The strongest relationship was between the clinician ratings and GHQ ($p<0.001$), followed by GHQ and CIDI ($p<0.002$) and finally CIDI and clinician ratings ($p<0.05$). It could be said with respect to this study that clinician ratings were in greater agreement with patient self-ratings, when compared to the ratings on a structured clinical interview administered by a non-clinician.

Thus, any community-based study of common mental disorders would do well to include apart from structured screening instruments and semi-structured interviews, a clinician rating of psychiatric caseness. This may especially be true when the disorder in question (such as epilepsy) may have unusual presentations of common mental disorder, or indeed, when the study concerned addresses multicultural populations.

2. EPIDEMIOLOGY OF EPILEPSY – AN OVERVIEW

2.1. Incidence and Prevalence

Epilepsy is the commonest serious neurological condition. Despite this, valid epidemiological indices have varied considerably in different studies. A number of factors have contributed to this discrepancy in figures; differences in inclusion criteria, classification, diagnosis and case ascertainment methods across studies; and the relative paucity of longitudinal studies, save a few examples in the west (Sander & Shorvon, 2002). While discrepant figures are a problem, generic to epidemiological studies of common medical disorders, there are problems peculiar to epilepsy that are reviewed here.

The incidence has been found to be around 50 cases per 100,000 persons, per year (with a range of 40–70/100,000/year). The figure given for developing countries is generally higher in the range of 100–190/100,000/year (Hauser, 1998; McDonald et al., 2000). A large population-based study in Ecuador identified all individuals with a history of seizures, including those with newly diagnosed non-febrile seizures (acute symptomatic seizures were included) and some children with multiple febrile seizures. The incidence was higher than many other reports 190/100,000 based on the number of persons with seizures seen in the year before the survey, although the incidence of neurologically confirmed cases was 30% lower (Placencia et al., 1992).

The usual prevalence figure given is about 5–10 cases per 1000 persons, excluding febrile convulsions, single seizures and inactive cases. The lifetime prevalence of seizures (the risk of having a non-febrile epileptic seizure at some point in an average lifetime) is between 2 and 5%. This difference between lifetime

prevalence and active epilepsy indicates that the majority of patients either go into remission or die (Sander & Shorvon, 2000).

2.1.1. Age Specific Incidence & Prevalence

Epilepsy is a disease with onset at extremes of life, at least in industrialised countries. Where provided, age-specific incidence is consistently high in the youngest age groups, with the highest incidence occurring during the first few months of life. Incidence falls dramatically after the first year, and remains stable until adolescence, when it falls again (Hauser et al., 1993; Camfield & Camfield, 1994). In most industrialised countries, age specific incidence is lowest during the adult years, and increases again in old age, populations over 70 having a greater risk than children (Hauser, 1998; Sander & Shorvon, 2002).

Age adjusted prevalence per 1000 population has varied greatly from 3.6 to 41.3, even in studies involving similar methodologies, protocols, and even investigators. Stringent case verification procedures may explain some differences as demonstrated in the study in Ecuador, in part (Placencia et al., 1992). When active prevalence (number of active cases) as opposed to lifetime prevalence is studied, a pattern of increasing active prevalence observed with each subsequent age group, with the highest prevalence occurring in the elderly, as demonstrated in both the Rochester (Hauser et al., 1991) and Icelandic (Olaffson et al., 1996).

2.2. Risk Factors

Most population-based studies of epilepsy provide information regarding presumed aetiology. While definitions for inclusion are seldom provided, the proportion of cases with an identified antecedent (remote symptomatic epilepsy) is relatively consistent, ranging from roughly a quarter to a third of all patients surveyed. In children, epilepsy associated with neurological deficits from birth is the most important single aetiological relationship, whereas cerebrovascular disease is the most commonly identified cause among adults (Hauser, 1998).

Brain trauma, stroke, central nervous system infection, and degenerative brain disease are readily identified as antecedents of epilepsy. While specific causes are noted in certain geographical regions, a definitive cause is identified in only one-third of newly identified cases. There are interesting contrasts between developed and developing nations with cerebrovascular disease being the commonest cause in the former (Hauser et al., 1993) and CNS infections, cerebral palsy (especially in children) in the latter (Carpio & Hauser, 1993). However, even in incidence studies in endemic areas, neurocysticercosis only accounts for a small proportion of newly diagnosed cases (Diaz et al., 1992) raising questions about the importance of such factors.

Epidemiological studies have helped to confirm the role of these factors and to quantitate the risk. Thus the risk of epilepsy in someone with a penetrating head injury acquired during military service is more than 500 times than that expected in general populations (Salazar et al., 1985). In contrast, those with a history of head

injury with loss of consciousness or amnesia of less than 30 minutes, have no increase in risk (Annegers et al., 1980). While stroke closely follows head injury with a risk ratio of 20; brain infections such as encephalitis and meningitis have a risk ratio of 16 and 10 respectively; degenerative brain disorders like Alzheimer's disease, hypertension and heart disease, neurological disorders like Multiple sclerosis, depression, alcohol and substance abuse, all have risk ratios between 10 and 3; with psychotropic drugs and treatments, tricyclic drugs, neuroleptics, electroconvulsive therapy (ECT) only marginally increasing the risk (1.5) (Hauser, 1998).

While there is a continued belief that adverse prenatal and perinatal events are associated with an increased risk of epilepsy, it has not been demonstrated at least in the developed world that these factors increase the risk of epilepsy, in the absence of neurological handicap. Epidemiological evidence also does not support a causal association between febrile convulsions and epilepsy (Hauser, 1998). While over 200 syndromes in which seizures are a part of the phenotype have been identified, these largely follow simple inheritance patterns, and are mostly rare or indeed very rare, accounting for only 1% of all epilepsy. These include neurocutaneous, neurodegenerative, inherited metabolic disorders and inherited malformations of cortical development. On the other hand, epilepsies with predominantly a complex genetic predisposition are common and account for about 50% of all genetically based epilepsies (Johnson & Sander, 2001). Thus, most common hereditary epilepsies exhibit a complex pattern of inheritance and are either examples of polygenic disorders or multifactorial inheritance.

Although genetic research in epilepsy is developing exponentially, in the absence of other information it has been proposed that epilepsy in a first-degree relative increases the risk three-fold (Annegers, 1982). The absolute increase is modified by which first-degree relative is affected (sibling, mother, father); the seizure type and aetiology of epilepsy in the affected relative, and the electroencephalographic pattern in the relative or individual in question (Hauser, 1998).

2.3. Natural History

Prognosis in epilepsy is the prospect of attaining seizure freedom once epilepsy has been established. Seventy to eighty per cent of people developing epilepsy will remit, while the remaining continue to have seizures despite optimum treatment. Remission usually occurs within the first 5-year period, and for most people therefore, epilepsy is a relatively short-lived condition (Sander, 1993; 1995).

2.3.1. Recurrence After the First Seizure

While earlier recurrence studies suggested that most patients with a single seizure had no further attacks, the incidence of epilepsy in population studies is greater than that of single seizures. Estimates of the risk of recurrence after the first seizure have varied from 27% to 81% (Hart et al., 1990; Berg & Shinnar, 1991), with estimates at the lower end of the range being derived from hospital-based studies, while estimates from community studies are at the top level.

It has been suggested that this variation may be an effect of "the time of entry to the study" bias (Sander, 2003). As the risk of seizure recurrence is greater in the weeks following the initial seizure (Sander, 1993,1995; Sander & Sillanpaa, 1998), a prolonged interval between the initial seizure and recruitment into a study may result in the second seizure having already occurred, leading to the patient not being included, and thus an underestimated recurrence risk. A large hospital-based study clearly showed this: a recurrence rate of 15% was reported among patients registered after eight weeks of their first seizure compared to 50% in patients registered within the first four weeks (Hopkins et al., 1988).

The impact of treatment on the risk of recurrence has been assessed in only a few studies. In one study, patients were randomised either to treatment, or to no-treatment after a first convulsion (First Seizure Trial Group, 1993). Recurrence at 24 months in the treated group was 26% compared to 51% for those untreated. The impact of early treatment on the long-term prognosis of epilepsy remains poorly understood.

2.3.2. The Natural History of Treated Epilepsy

2.3.2.1. Newly Diagnosed Epilepsy

There have been a number of hospital-based prospective studies reporting the effect of treatment in newly diagnosed cases (Sander & Sillanpaa, 1998). Overall, the 1-year-remission rates in these studies have varied between 58–95%, with most studies reporting rates between 65–80%.

The prognosis for remission of partial seizures is less good. In one large study, complex partial seizures were controlled in only 16–43% of patients, while those with only secondarily generalised attacks control this was achieved in 48–53% at one year (Mattson et al., 1985). Most studies have reported outcome to be less favourable in patients with multiple seizure types, associated neurological deficit and behavioural or psychiatric disturbance (Sander & Sillanpaa, 1998).

Two large community-based studies have looked into the long-term remission of treated epilepsy. In Rochester, 15 years after onset, 76% of patients were in a five-year remission (Annegers et al., 1979). In Kent, 73% of patients entered remission (Goodridge & Shorvon, 1983). In both studies, most patients who entered remission did so in the first 2 years and as time elapsed, the prospect of entering remission decreased.

2.3.2.2. Chronic Epilepsy

All hospital studies of newly diagnosed epilepsy have consistently demonstrated that 20–30% of patients do not enter remission (Sander & Sillanpaa, 1998). This has been confirmed by community studies (Annegers et al., 1979; Goodridge & Shorvon, 1983).

2.3.2.2.1. Drug Withdrawal and Seizure Relapse

Seventy to eighty percent of patients on AED treatment will eventually become seizure-free (Sander; 1993, 1995). As AEDs have long-term side effects, withdrawal is considered after a substantial remission period. There are, however, risks of relapse in doing so. The probability of relapse has varied between 11–41% (Sander, 2003).

A number of risk factors for seizure recurrence after discontinuation of treatment have been identified (MRC, 1991; Berg & Shinnar, 1994). These include a long history of seizures before remission, more than one seizure type, the presence of a structural brain lesion, the presence of abnormal neurological signs, a past history of remission and relapses and juvenile myoclonic epilepsy. Whether EEG is helpful in predicting recurrence remains controversial in adults. In children, however, the presence of slow background rhythms or frankly, abnormal discharges in the record indicates an increased risk of recurrence.

2.3.3. The Natural History of Untreated Epilepsy

As outcome studies of epilepsy have almost invariably been of the treated condition, the probability of spontaneous remission in an individual patient and the effect of early treatment on the outcome remain unknown (Sander, 2003).

2.3.3.1. Spontaneous Remission

Patients with epilepsy in developing countries may have had untreated epilepsy for long periods of time (Sander; 1993, 1995). If these patients were to never remit, the prevalence rate for epilepsy in developing countries would be much higher than those found in the developed world (5–10/1,000) (Sander & Shorvon, 1996). While some studies in developing countries have reported higher prevalence rates for epilepsy, these have generally been small studies involving selected populations, possibly with higher rates of degenerative CNS disease, parasitic infestation or specific epileptic syndromes (Sander & Shorvon, 1996).

Further, large prevalence studies in largely untreated populations in developing countries have reported similar rates to those found in the developed countries (Bharucha et al., 1988; Li et al., 1985; Placencia et al., 1992). While this may be because epilepsy leads to higher mortality rates in these countries, it is unlikely to account for the whole difference. Lack of optimal case ascertainment procedures for active seizures, or indeed missing cases in remission rather than active cases, may explain these results (Sander, 1993; Sander & Shorvon, 1996). A more plausible explanation would be that some of the patients do enter spontaneous remission. Two small retrospective studies, one carried in a hospital clinic in Finland (Keranen & Riekkinen, 1993) and the other in a rural community in Southern India (Mani et al., 1993) seem to support this explanation: both reported a remission rate of 50% in untreated patients.

2.3.3.2. Effects of Early AED Treatment on Prognosis

Observations on the efficacy of treatment in patients with chronic epilepsy who had not previously received AED treatment have now been made in 3 different studies in the developing countries (Watts, 1992; Feksi et al., 1991; Placencia, 1993). These studies involving more than 1,000 patients, have found that neither the duration of the condition nor the number of seizures before treatment were predictors of outcome. This offers some evidence against the view that unless treatment is given early, chronic epilepsy will develop.

2.3.4. Prognosis

Sander (2003) has classified epileptic syndromes into four groups based on prognosis. These groups are to some extent static and self-contained, and migration from one group to another is unlikely unless new factors arise, for instance exposure to a novel AED, surgical intervention, or the widening of a lesion. Patients will fall in to one of these prognostic groups and this is likely to be pre-determined by the epileptic syndrome.

2.3.4.1. Excellent Prognosis

In this group syndromes and conditions are self-limiting and very benign. They may comprise about 20–30% of all people who develop epileptic attacks. Usually, only a few seizures occur. Patients commonly do not require AED treatment, as spontaneous remission is the rule. Conditions include benign neonatal convulsions, fifth-day

seizures, the benign partial epilepsies, and benign myoclonic epilepsy of infancy and some of the epilepsies with seizures precipitated by specific modes of activation (acute symptomatic seizures).

2.3.4.2. Good Prognosis

Epilepsies in this group are usually benign, are short lived and may comprise about 30–40% of all people who develop epileptic attacks. Seizures are easily controlled with AEDs. Once remission is achieved, this is permanent and AEDs can be successfully tapered off. It could be argued that in this group AEDs are curative or suppressant until the epileptic diathesis resolves spontaneously. Conditions include childhood absence epilepsy, epilepsy with generalised tonic clonic seizures on awakening, non-specific generalised tonic clonic seizures in patients with no neurological signs, and some of the localisation-related epilepsies (both cryptogenic and symptomatic types).

2.3.4.3. Uncertain Prognosis

In this group, there is a long-term tendency to seizures, and it comprises about 10–20% of people who develop epilepsy. Patients often remit with AED therapy but may relapse if AEDs are stopped, thus treatment usually is a lifetime prospect. Conditions include juvenile myoclonic epilepsy, and the bulk of the localisation-related epilepsies (both cryptogenic and symptomatic). Some patients in the latter group may, however, be amenable to surgical intervention, with subsequent change in prognostic group.

2.3.4.4. Bad Prognosis

This group comprises up to 20% of all people who develop epileptic attacks. AEDs in this group are palliative rather than suppressive of seizures. There is a continuous tendency for seizures, despite intensive treatment with all AEDs. Although, occasionally patients may move to the uncertain prognosis group when exposed to a novel AED. Some patients in this group may also be amenable to surgical intervention with subsequent change in prognostic group. Conditions include seizures associated with neurological deficit present from birth (tuberous sclerosis, Sturge-Weber, malformations, cerebral palsy, etc.), *epilepsia partialis continua*, progressive myoclonic epilepsies and other progressive neurological diseases, West Syndrome, Lennox–Gastaut Syndrome and others where atonic/tonic seizures are a prominent feature, localisation-related seizures associated with gross structural lesions and some of localisation-related cryptogenic epilepsies.

Thus, the outcome of epilepsy is determined to a large extent by its aetiology and studies reporting outcome need to be encouraged to classify all reported cases according to epileptic syndromes rather than seizure type (Sander, 2003).

2.4. Mortality

While epilepsy is often assumed to be a benign condition with relatively low mortality, there is considerable evidence to the contrary. Consistent increases have been reported in the mortality of people with epilepsy, especially younger patients and those with severe epilepsy (Sander, 2002).

Higher Standardised Mortality Ratios (SMR) have been reported for males when compared to females, the highest SMRs being in the 0-40 year age group, and the lowest SMRs being in the 75+ age group. Two community studies found overall SMRs to be 2–3 times higher than those of the general population, the risk being largely limited to the first 10 years after diagnosis (Hauser et al., 1980; Lhatoo et al., 2001). This may suggest that increased mortality was due to the underlying cause of epilepsy (brain tumours, head injury, vascular events etc.) rather than due to any other factor (Sander, 2002).

Seizure type seems to play a role – both partial and complex partial seizures alone are not associated with an increased SMR when compared with general population. Although those in remission have been shown to be at higher risk in some studies (Sander, 2002). Primary or secondary generalised seizures have a higher SMR – 2.4 overall but 3.5 in the first year after diagnosis, with myoclonic seizures being highest at 4.1 (Hauser et al., 1980; Lhatoo et al., 2001). Severity of epilepsy has been shown to increase risk of mortality in some studies (Sander, 2002). Higher mortality rates for non-Caucasian populations have been reported in America, although this may be a reflection of socio-economic status, rather than a true biological increase (Chandra et al., 1994).

Causes of death in epilepsy include bronchopneumonia, which is strongly associated with epilepsy irrespective of age, and cancer the SMR and PMR for which are consistently elevated, even after primary brain tumours have been excluded. Some studies have linked this excess mortality to the diagnosis of neoplasm preceding the diagnosis of epilepsy rather than the other way around (Chandra et al., 1994;

Klenerman et al., 1993). A high score of hepatobiliary neoplasm has been reported in studies of small selected institutionalised groups (Klenerman et al., 1993).

Deaths directly related to epilepsy are sub-divided into the following categories: status epilepticus, sudden unexpected death (SUDEP) and accidents. Status epilepticus has a high fatality rate of between 10–20%, although studies have failed to differentiate between individuals with epilepsy, and those who had no previous seizures. SUDEP is defined as a non-traumatic unwitnessed death occurring in a person with epilepsy, who had been previously healthy and for whom no cause of death is found even after a thorough post-mortem examination (Lathers & Schraeder, 1990). Explanations include suffocation during a seizure, deleterious effects of AEDs, autonomic seizures affecting the heart, cardiac arrhythmias and the release of endogenous opioids, although a single pathogenic mechanism remains elusive. Frequent convulsive seizures, lack of nighttime supervision, use of more than one AED, frequent visits to Accident and Emergency Departments, have all been identified as risk factors. Annual mortality rates of sudden death have varied from one per 200/ one per 370, depending on the population studied (Sander, 2002).

People with epilepsy have a higher risk of accidents, drowning and suicide. AEDs may contribute to the increased mortality although evidence in this regard is not robust, and barbiturates and hydantoins have been shown to have oncogenic potential (Sander, 2002).

2.5. Methodological Problems in Epidemiological Studies of Epilepsy

Differences in inclusion criteria, classification, diagnosis, and case ascertainment methods have led to considerable variations in incidence and prevalence figures, and will be discussed in detail herein.

2.5.1. Case Ascertainment

2.5.1.1. Deficiencies in Patient Reporting

Unlike many other ailments, the bulk of seizure disorders do not have physical manifestations, and are of a transient and unpredictable nature (Sander & Shorvon, 1987). The diagnosis is based on "history" or "chance observation of a seizure", both of which have inherent problems. Patients may often be unaware of their symptoms, misinterpret them, fail to report these due to misperception and other such factors, or even in some cases conceal them due to the significant stigma attached to the condition. Social customs also influence the reporting and diagnosis of epilepsy. For e.g., in places like Japan where families sleep together, there may be a higher reporting of seizures in their offspring by the mothers (Tsuboi, 1984). Under reporting is not confined to developing nations however, and studies in Metropolitan London (Hopkins & Scrambler, 1977) and Newcastle upon Tyne (Miller et al., 1960), and Japan (Tsuboi, 1984) have shown that 14–20% of children with epilepsy had never consulted a doctor. Therefore, To be comprehensive, community studies should be independent of pre-existing medical records and use a highly sensitive questionnaire (Sander & Shorvon, 1987).

2.5.1.2. Deficiencies in Seizure Diagnosis

The diagnosis of epilepsy as noted previously is essentially clinical, and may therefore be both difficult and delayed. The differential diagnosis encompasses the gamut of disorders with transient alterations of consciousness, and in practice, both false positive and false negative diagnoses are common (Sander & Shorvon, 1987). Syncope is frequently misdiagnosed as epilepsy (Sisodiya, 2002), as are non-epileptic seizures, which are misdiagnosed as epilepsy in 5–20% of cases (Betts, 2002) and often have psychogenic origins. In a study of 106 newly diagnosed hospital cases, 24 months had elapsed before a correct diagnosis was made in 25% of cases and this may have an impact on incidence and prevalence (Shorvon, 1982). However, many epidemiological surveys fail to acknowledge this problem, and a number of studies rely upon loosely defined diagnostic criteria and specialist opinion, an approach that researchers in other chronic disorders have chosen to reject (Sander & Shorvon, 1987).

2.5.1.3. Case Ascertainment Methods

The most common published method of ascertainment is the retrospective reviews, which are sources of inaccuracy and under-reporting (Zielenski, 1974). Case records are usually reviewed for a mention of fits/seizures/epilepsy; prescription of anticonvulsants; request for EEG; or a diagnostic index is used. Differing diagnostic and therapeutic practices and temporal changes within or between different centres are invariably ignored (Sander & Shorvon, 1987). A retrospective record review may be followed by an interview of positively identified cases. A case register is another

method, which, if established with careful precautions, has advantages over the retrospective record reviews. Other approaches include: house–house surveys which have the advantage of being prospective, and not relying on prior diagnosis that are both expensive and time consuming; the use of public health, school or institutional records to conduct a survey. However, these surveys depend upon screening questionnaires and trained health personnel (not medically qualified), and in the absence of well-validated instruments can produce fallacious results.

2.5.2. Classification and Case Definition

Cases are commonly classified based on seizure type and aetiology. However, accurate classification is dependant on good history taking and observation, as well as in-depth knowledge of the system in use. Laboratory tests such as the EEG may contribute to diagnosis but cannot confirm this.

In epidemiological studies, it is important to follow an international classification system and fixed criteria upon which the diagnosis of seizures could be made. An internationally agreed classification of seizure type has been proposed which incorporates EEG data (ILAE, 1981). In designing an epidemiological study it must be borne in mind that hospital specialists in the face of EEG evidence often fail to agree with each other (Lavy et al., 1972). Classification by aetiology is interesting and may achieve importance in specific locations, such as the study of neurocysticercosis in parts of Central and South America. It is evident however, that the successful detection of an aetiological factor depends on the extent of

investigation and unless this is standardised and specified in any large-scale study, evaluation can be problematic (Sander & Shorvon, 1987).

A further methodological issue is the definition of epilepsy. If single seizures, neonatal seizures, febrile seizures and seizures in acute illnesses are included, the incidence and prevalence figures may be elevated several fold (Sander & Shorvon, 2002). Indeed, one difficulty is that many published reports in the past failed to include this crucial piece of information. Further, the issue of active versus inactive seizures had plagued epilepsy research for years. There were proponents of the view "once an epileptic, always an epileptic" (Lennox, 1960), which is contrary to evidence from epidemiological studies reviewed herein. The guidelines for epidemiological studies in epilepsy proposed by the ILAE and reviewed herein (ILAE, 1993), have clearly defined active epilepsy as at least one epileptic seizure in the past five years regardless of anti-epileptic treatment, which has to some extent put an end to this debate.

2.5.3. Selection Bias

Even with satisfactory ascertainment, classification and case definition, population selection bias may influence study results. There most certainly are regional differences in vital statistics reflecting geographic, ethnic and genetic, environmental and socio-economic factors. For this reason the demographic characteristics of the population should be well described, and the analysis should account for such differences. It is also important to avoid obvious errors such as sampling a selected population (those in an institution or those selected into the armed services for

example) or sample in areas that are endemic for any disease factor under study (neurocysticercosis for example). Age standardisation of data is important, as is the assessment of the natural history of the illness and the role of treatment (Sander & Shorvon, 1987).

2.6. ILAE Guidelines for Epidemiological Studies on Epilepsy

The International League Against Epilepsy (ILAE) established a Commission on Epidemiology and prognosis under the chairmanship of Dr. Pierre Jallon from Geneva, Switzerland. The guidelines proposed by this commission (ILAE, 1993) are summarised herein:

The first step in field studies is the use of a screening instrument adapted to the population at risk. The sensitivity and specificity of the questionnaire must be tested and validated, and the methods clearly described.

The diagnosis of epilepsy in epidemiological studies is clinical and should be derived by medical history, seizure description, and neurological examination, by an experienced medical professional using standardised diagnostic criteria.

Rigorous definitions are important: the categories being epileptic seizure, epilepsy, status epilepticus, active epilepsy, epilepsy in remission with/without treatment, febrile seizure, neonatal seizure, febrile seizure with neonatal seizure and non-epileptic events. Epilepsy is defined as "a condition characterised by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause.

Multiple seizures occurring in a 24-hour period are considered a single event. An episode of status epilepticus is considered a single event. Individuals who have only febrile seizures/neonatal seizures as herein defined are excluded from this category". A prevalent case with active epilepsy is defined as "a person with epilepsy who has had at least one epileptic seizure in the past five years, regardless of AED treatment". A case under treatment is someone with correct diagnosis of epilepsy receiving (or having received) AEDs on prevalence day.

For the purpose of an epidemiological study, the detailed ILAE classification may be too extensive. A clinical classification is thus proposed with seizures being classified into four categories: generalised (including tonic, clonic, tonic-clonic, myoclonic, absence); partial (simple partial, complex partial, partial epileptic seizure of unknown type, partial seizure-secondarily generalised); multiple seizure types (when each type is described); and unclassified when information is inadequate.

Epileptic seizures are also divided into provoked and unprovoked based on whether a precipitating insult is perceived. Provoked seizures are also called acute symptomatic seizures and occur in temporal correlation with a CNS insult or injury. Unprovoked seizures are categorised into remote symptomatic (static insult such as infection, cerebral trauma, cerebrovascular disease) or unprovoked seizures of unknown aetiology. The latter is sub-divided into idiopathic (to indicate certain partial and generalised epilepsy syndromes with particular clinical and EEG findings, and known cause as commonly believed) and cryptogenic which is used to include partial or generalised unprovoked epilepsies in which no factor associated with increased risk of seizures has been identified.

A few epidemiological indices are recommended: Point prevalence, period prevalence, lifetime prevalence, incidence, incidence rate, incidence density, cumulative incidence and standardised mortality ratio.

3. PSYCHIATRIC CO-MORBIDITY IN EPILEPSY

3.1. Historical Introduction

3.1.1. Pre-nineteenth Century Literature

The interface between epilepsy and psychiatry has a long and chequered history. Both have links with god, demons and witches, and the supernatural; and have evoked prejudice, disaffection and malediction from other members of society (Trimble, 1991).

The Greeks referred to epilepsy as "the sacred disease". The earliest writings were those of Hippocrates (460–377 BC) (Adams, 1939), who in his monograph "On the Sacred Disease" opined that it was a natural affection, with a hereditary origin, with its pathogenesis in the brain. The brain was thus the seat of both the falling sickness and madness, and both were related to the phlegm (Trimble, 1991).

There are several other examples from this period that link epilepsy and behaviour. The story of Hercules, whose birth was delayed by Hera, in order to favour the earlier delivery and succession of Eurystheus to the throne of Greece, has been alluded to in the writings of both Hippocrates and Aristotle. Hercules is believed to have killed his own children in a "seizure" of madness. The supposition that this was epileptic, relates to a Hippocratic treatise: "when the uterus is near the liver and the hypochondrium and produces suffocation, the woman turns up the white of her eyes, become cold, gnashes her teeth, saliva flows into her mouth, and she resembles the persons seized by a Herculean disease" (Temkin, 1971). Aristotle, in a treatise that considered "why talented individuals are melancholic?" gives Hercules as an

example: 'For he apparently had this constitution and therefore epileptic afflictions were called after him "the sacred disease" by ancients' (Simon, 1978).

This relationship between epilepsy and melancholia was also referred to by Hippocrates who stated, "Melancholics ordinarily become epileptics, and epileptics melancholics. what determines the preference is the direction the malady takes: if it bears upon the body, epilepsy, if upon the intelligence, melancholy" (Lewis, 1934). These ideas link with the Galenic concept of humours and their relationship with temperament. According to Galen, Temperament was a somatic rather than psychological state, and was derived by a combination of the four basic humours – phlegm, blood, black bile and yellow bile. Melancholia was related to black bile, but was also related to "raving", and to epilepsy (Trimble, 1991). For Galen the two had a related pathogenesis: "This humour arises in some people in large quantity either because of their original humoural constitution or their customary diet which is transformed into this humour by digestion in the blood vessels. Like thick phlegm, this heavy atrabilious blood obstructs the passage through the middle or posterior cavity of the brain and sometimes causes epilepsy. When its excess pervades the brain matter itself, it causes melancholy" (Siegel, 1973). The perception of epilepsy in conjunction with other periodic afflictions including varieties of mental illness, all linked to the moon was also prevalent among the Romans. This led to the condition being referred to as *morbidus lunaticus* and to the development of the term "lunatic".

These early writings linking epilepsy and mental illness notwithstanding, with the waning of Greek influence on Roman scholars, there were no new advances in medical thinking, until the Renaissance (Trimble, 1991). Some of the focus during

this period shifted to the Arab world, where too, associations between epilepsy, mental illness, and demons remained. Some very good descriptions linking religiosity, epilepsy and mental illness emerged during this period, the visions of many soothsayers and prophets being alluded to as manifestations of epilepsy. Both Mohammed (Howden, 1873) and Saint Paul of Tarsus (Landsborough, 1987) are examples of religious prophets who were described to periodically hear voices and fall to the ground. There is thus considerable ancient literature emphasising the associations between epilepsy, ecstasy and prophecy (Temkin, 1971).

The links between the demons, the moon and epilepsy, continued into the 18th century. They extended far beyond lay and theological considerations into the writings of such physicians as Stahl (1695–1734), Hoffman (1660–1742), van Swieten (1700–1772) and even Willis (1621–1675) (Trimble, 1991). Allusions to the devil (Harle, 1729) and the moon (Mead, 1746) were commonplace during this period. The first substantial treatise on epilepsy published by Tissot (1770), opposed ideas about lunar influences, but linked epilepsy to masturbation. These ideas had a profound influence on epilepsy for years to come, and were linked to the introduction of bromides for the treatment of the condition. Similarly, the link between masturbation and mental illness too lived on for generations (Trimble, 1991).

3.1.1.1. Epilepsy & Psychiatry in the 19th and Early 20th Centuries

The growth of hospitals, led to patients with epilepsy previously incarcerated in prisons (along with the insane), to occupy several hospital wards. Epilepsy was a particularly common diagnosis in asylums, and in some, epileptics were segregated in separate wards. While many older asylums excluded patients with epilepsy especially when it was associated with insanity. The prognosis of the condition believed to be particularly poor in that case (Griesinger, 1857), county asylums that were built later did accept patients with epilepsy. The Commissioners in Lunacy reported that in 1887 there were 1,294 patients with epilepsy in various asylums in England and Wales, from a total of 14,336 and 9% of insane patients brought under treatment that year had epilepsy (Savage, 1892).

This concentration on patients in asylums had some interesting consequences. The first was that, patients were subjected to close medical scrutiny and this led to a number of interesting observational studies and findings thereof. Second, the policies of the day meant that, the more severely affected patients with epilepsy were looked after and followed up by psychiatrists in asylums, and those with less severe forms of the illness remained in the community, and were treated by general physicians and neurologists of the day (Trimble, 1991).

At this time a greater recognition of the mental health problems that afflicted patients with epilepsy also became more evident. Pinel, a leading physician in Paris (credited with Tuke and Connolly for the so-called unchaining of patients in the asylum-workhouses), noted that insanity complicated with epilepsy was a frequent

problem, and that the prognosis was poor. He advocated the separation of patients with epilepsy, and went on to prescribe special procedures for their care.

However, it was in Germany that a considerable literature evolved during this period. The German psychiatrists in that period were all somatics rather psychics, which essentially means that they believed in the organic basis of mental disorder (Schmitz, 1998). Flemming (1859) had a special interest in alternating states of epilepsy and insanity, and in his influential textbook, Pathology and Therapy of Psychoses observed "Epilepsy and mental disorder are two states of illness of the very closest relationship; they represent identical pathological conditions in two different areas of the nervous system". While Friedrich Hoffman (1862) introduced the term "epileptic equivalents" for mental disorder in epilepsy, Heindrich Hoffman (1859) recognised that epilepsy and mental disorder often develop into one another.

Following on from the influential works of Griesinger (1868), Samt (1875, 1876) developed a bewildering classification of epilepsy with 12 categories. He re-introduced the term "epileptic equivalents" and was convinced that, this was a highly specific category with clinically proven seizures not being mandatory for diagnosis. Sommer (1881) in the same period acknowledging the concept of equivalents in people with epilepsy, with the exception of those who did not have clear aetiological antecedents, suggested the term "psychic status epilepticus" or "epileptic rudiment" for these states. There was considerable disagreement among these "experts" which is documented in elegant reviews by Trimble (1991) and Schmitz (1992, 1998).

By the beginning of the 20th century, the case of epilepsy was being taken over by neurologists, and the emphasis had shifted to the classification of seizures and their treatment. Important contributions in this period came from authors such as Bonhoeffer (1909) who in a discussion on epileptic equivalents and their specific psychopathology described the non-specific presentation and multiple aetiologies of organic psychosis (acute exogenous reaction). The nature of the relationship between epilepsy and schizophrenia was discussed extensively in the context of unitary vs. combined, composite or hybrid psychosis.

Kraepelin, the outstanding pioneer of the modern psychiatric classification, succeeded in identifying most of the psychiatric disorders of epilepsy that can be presently recognized (Kraepelin, 1923). Kraepelin pointed out that all psychiatric changes manifest in the preictal or postictal phases may also occur interictally, independent of convulsive events, thus indicating their kinship; seizures may also appear interspersed in the course of the psychiatric disorders. The most commonly encountered interictal dysphoric episodes (Verstimmungen) are characterized by irritability, depressive and at times euphoric moods, anxiety, headaches, and insomnia. They occurred in like manner every few days to every few months and lasted for a few hours up to two days. The same dysphoric symptoms also can be observed in the prodrome of a seizure or postictally. Kraepelin then noted dysphoric episodes with psychotic symptoms, i.e., interictal events with hallucinatory or delusional content developing as expansions of dysphoric episodes. These psychotic episodes usually occurred in clear consciousness and lasted a mere few days; only in isolated cases the psychotic state persisted for weeks or even months and may then superficially look highly similar to certain forms of dementia praecox. More

prominent among the psychotic episodes of epilepsy at that time, were confusional–amnestic episodes with clouded consciousness termed twilight states (Dämmerzustände), lasting for mere hours to at the most 1/2 weeks. They were chiefly observed subsequent to seizures (at times following a brief lucid interval), at times preictally, and occasionally independent of observed seizures. Dysphoric symptoms were marked during the twilight states, with episodes of violent rage, or extreme anxiety, or impulsive suicide attempts; exalted religious states were often observed. Kraepelin noted that it was difficult to distinguish different forms of the twilight states. Finally, Kraepelin defined personality changes (Verblödung) characterized by slow-viscous and circumstantial mental processes, and by a highly ethical and helpful attitude with an unusual predilection for religious ideas that contrasted starkly with the episodic irritability and tendency to explosive fury. Kraepelin's findings are of particular importance because they document the psychopathology of epilepsy before effective antiepileptic drugs were available (Blumer, personal communication).

An important contribution in this period came from the work of Laszlo von Meduna, who postulated a biological antagonism between epilepsy and schizophrenia based on his observations that true combinations of these disorders occurred in only one out of 6000 psychiatric cases. Better prognosis in those with the combination than those with pure epilepsy, and observations in numerous case studies (including his own) that patients experienced a remission of psychotic symptoms following spontaneous epileptic seizures. Meduna's writings have been criticised as being flawed (Schmitz, 1998); however it has been suggested that he believed in a syndromic affinity between epilepsy and schizophrenia, and an antagonism between

symptoms, psychosis and seizures (Wolf & Trimble, 1985). Nevertheless, Meduna (1935) did successfully introduce convulsive therapy for psychosis with camphor injections, and the rest as they say is history!

Other important and rather startling contributions were to follow: The introduction of the EEG as a diagnostic tool revolutionised research in this area, as did the introduction of new drugs such as Ethosuximide. Heinrich Landoldt re-discovered epileptic equivalents using this tool, and his work prompted a lively discussion, which is well reviewed in the contemporary essays by Janz (1969, 1997, 1998). In a careful study combining clinical and EEG parameters in a series of patients with epilepsy and behavioural symptoms Landolt (1953, 1958) identified four types of distinct psychotic episodes: Post-paroxysmal twilight states, the petit mal-status of Lennox, productive psychotic episodes with "forced normalization" of the EEG, episodes with an increase of electroencephalographic pathology (psycho–organic episodes). It was Landolt's description of normal electroencephalograms in association with psychotic illness, the forced or paradoxical normalization of the EEG with psychotic episodes, which renewed interest in the potential antagonisms between seizures and psychosis that drew the greatest attention.

Soon after, Dongier (1959) published the results of a European study on the clinical and EEG phenomena of psychosis in epilepsy. She studied the relationship between clinical and EEG features and patterns of psychopathology. In this study patients with centrencephalic epilepsy were as likely as those with psychomotor epilepsy to develop psychotic episodes. Patients in the centrencephalic group had associated confusional states and psychotic symptoms that were largely transient with

characteristic EEG features. On the other hand, patients in the psychomotor group did not suffer from confusion, had more prolonged episodes of psychosis, and demonstrated more affective and anxiety features.

3.1.1.2. Contemporary Research in the 20th Century

Slater and Beard (1963) published their classic five-part paper on the schizophrenia like psychoses of epilepsy. Following on from the work of Bartlett (1957), Denis Hill (1953), Desmond Pond (1957) and others, these authors systematically examined 69 patients with epileptic psychoses – 31 from the National Hospital for Neurology and Neurosurgery, and 38 from the Maudsley Hospital, both in London (UK). In all cases thus included, the diagnosis of epilepsy was supported by EEG, the diagnosis of schizophrenia made by an experienced psychiatrist and in the authors' opinion, schizophrenia would have been the diagnosis of choice in the absence of epilepsy. Based on their results the authors opined that the combination was not due to chance. The pre-morbid personality was normal but showed evidence of change in the pre-psychotic period; both long duration and increased frequency of epilepsy were associated with the development of psychotic symptoms; although the onset of psychoses was generally unrelated to seizures, in a proportion of cases a falling frequency of seizures before psychotic symptoms began was noted; insidious onset and chronic course were frequent; the full spectrum of schizophrenic symptoms were observed with no special distinguishing features. This paper, although in a highly selected population, was the first to study a reasonable large sample of patients with schizophrenia like psychoses of epilepsy, using a contemporary research approach.

Flor Henry (1969) set about trying to investigate the link between epileptic psychoses and the epileptic process. Fifty patients with psychoses of epilepsy drawn from the Maudsley Hospital were compared with 50 controls randomly chosen from neurology wards with EEG evidence of temporal lobe disturbance. The two groups were compared across 71 variables designed to evaluate according to the author – sociological, personality, epileptic, psychiatric, genetic, neurological, electrophysiological, and psychometric characteristics of the two populations. Patients with psychosis were found to have fewer psychomotor/psycho-sensory seizures; experience convulsive/ictal manifestations less frequently; have epilepsy literalised to the dominant hemisphere; have an excess of bilateral foci; have fewer minor temporal seizures. Further patients with schizophrenia like psychoses, when compared to those with affective psychoses were found to have greater evidence of brain damage and preponderance of epilepsy literalised to the non-dominant hemisphere. This study confirmed several observations of Dongier, and provided further evidence for Landolt's observations on Forced Normalization, and the later description of alternative psychoses (in the absence of EEG evidence of forced normalization) by Tellenbach (1969).

Significant literature that has followed these early efforts, is reviewed in the section on Neuropsychiatric epidemiology.

3.2. Neuropsychiatric Epidemiology in Epilepsy

Although the interface between epilepsy and psychiatry has stimulated considerable interest (and research) over the years, much of this has been in the hospital and in institutional populations. There have been very few studies conducted in representative populations in the community, and epidemiological data is scant. The paucity of epidemiological research at this interface is in stark contrast with developments both in epilepsy per se, and in mental health research. The epidemiology of epilepsy has been well studied in many countries and considerable data, both descriptive and analytical (reviewed in section 2 and elsewhere – see Hauser, 1998 for example) are now available. Indeed, epilepsy has been subjected to the gamut of epidemiological research including cross-sectional, case-control and cohort studies (Hauser, 1998).

Impressive developments have also taken place in the field of mental health epidemiology. Efforts by the World Health Organisation's Division of Mental Health, and other pioneering organisations around the world have led to a significant understanding of the epidemiology of psychiatric disorders. This has also led to the development of now universally accepted classificatory systems in psychiatry, such as the Diagnostic and Statistical Manual (DSM-IV) now in its fourth edition (APA, 1994), and the mental disorders component of the International Classification of Diseases, now in its tenth edition (ICD-10) (WHO, 1992a).

The commonly held conviction among epileptologists and neuropsychiatrists is that psychiatric disorders are not only common in epilepsy, but that distinct and

unique forms of psychopathology are prevalent Krishnamoorthy (2000). In the past three decades attention has been directed towards discrete forms of psychopathology in epilepsy such as the temporal lobe personality (Waxman and Geschwind; Bear and Fedio, 1977; Blumer, 2000), inter- and post-ictal psychosis (Trimble, 1992; Toone) and inter-ictal dysphoric disorder (Blumer 1995, 2000). This combined with the observation of similarities in behaviour during seizures and in psychopathological states has strengthened the notion of an affinity between epilepsy and psychiatric disorder. Yet, the evidence that psychiatric disorders are over represented in epilepsy is far from convincing, with conflicting results in different studies (Krishnamoorthy, 2001).

In this section, the Neuropsychiatric epidemiology of epilepsy is reviewed in three parts: first, the important and considerable interface between epilepsy and learning disability and the specific literature thereof; second, a review of studies in hospital and institutional populations which have included eclectic subject cohorts resident in these settings; and third, epidemiological studies of psychiatric co-morbidity in adult populations with epilepsy, resident in the community.

3.3. Neuropsychiatric Epidemiology at the Interface Between Epilepsy & Learning Disability

The literature with regard to epilepsy and psychiatric disorder in learning disabled populations is rather complex. In general, there is an over-representation of both epilepsy and behaviour problems in subjects with learning disability (LD). Community studies have indicated prevalence rates of epilepsy ranging from 6%

among children with mild LD (IQ 50–70) (Ross & Peckham, 1983), to 24% in severe LD (IQ <50) (Steffenberg et al., 1995) and 50% in profound LD (IQ <20) (Corbett, 1988). A reasonable global estimate therefore is that between 15% (mild LD with IQ>50) and 30% (severe LD- IQ <50) have co-morbid epilepsy (Sillanpaa, 1996).

On the other hand, it has been estimated that around 50% of subjects with LD in a hospital/institutional setting will pose management problems due to psychiatric disturbance. Affective and schizophrenic disorders, dementing syndromes, early childhood autism, hyperkinetic syndromes, neurotic, conduct and personality disorders, whether or not associated with epilepsy have been reported in this population (Reid, 1983).

3.3.1. Are Psychiatric Disorders Over-Represented in Subjects with LD and Epilepsy?

Given the background of high psychiatric co-morbidity in both LD and epilepsy, one would expect the burden of psychiatric co-morbidity to be significant in cases where both conditions co-exist. However, literature on psychopathology among subjects with epilepsy and LD is sparse and contradictory.

Rutter et al. (1970) in the Isle of Wight survey demonstrated clearly that there was an association between epilepsy and psychiatric disorder. They showed that while psychiatric morbidity was 6.6% in a control group of children, the figure rose to 11.6% with physical disorder and 34.3% with brain disorder. Further, in comparing two groups with brain lesions they also demonstrated that psychiatric co-morbidity was higher in the group with seizures (58.3%) than in the group that was seizure-free (37.5%).

Eyman et al. (1969) studied mentally handicapped populations in three large hospitals in the USA and reported that hyperactivity, aggression, problems with speech, and difficulties with eating/dressing were more common among institutionalised subjects with epilepsy and mental handicap. Capes and Moore (1970) compared 21 factors of maladaptive behaviour between 229 subjects with epilepsy and a non-matched control group of 511 in Arizona Children's Colony, and found significant differences in 16 out of 21 factors – hyperactivity, aggression and withdrawal in particular.

In another large population-based study, Lund (1985a) identified 324 mentally retarded adults in the county of Aarhus in Denmark, five of whom did not meet WHO criteria for mental retardation, and 17 of whom (mainly younger individuals living in the community) refused to take part. 302 individuals with mental retardation were examined with regard to epilepsy and psychiatric disorder using the Medical Research Council (MRC) schedule of handicaps, behaviours and skills (HBS) (Wing L., 1980) and a schedule of psychiatric symptoms (Lund L., 1985b). In 55 (18.2%) epileptic seizures had occurred some time during their lives, and in 25 (8.3%) in the last year before investigation (active epilepsy). Increasing degree of mental retardation was associated with an increased prevalence of epilepsy and psychiatric disorder. Psychiatric disorders were strongly correlated with epilepsy, with 56% of mentally handicapped persons with active epilepsy suffering from a psychiatric disorder, as compared with 26% of those without seizures, a statistically significant difference. However, this study failed to use a matched control group, which may in part explain these findings.

On the other hand, Corbett in the Camberwell Study (1981) did not find any significant difference in the frequency of behavioural disturbance, in comparing children with mental handicap with/without epilepsy. This latter study included patients in the community and in both hospital and non-hospital care. This finding was also supported by Deb et al. (1987) who failed to find any difference in the rates of maladaptive behaviour when they compared adults with epilepsy with a matched group of adults without epilepsy in a mental handicap institution. Similar findings were also reported in a study by Espie et al. (1989) that compared behaviour among people with mental handicap and epilepsy who lived in the community and attended day centres.

Deb and Hunter in a series of papers (1991a,b,c) reported studies of maladaptive behaviour, psychiatric illness and personality disorders in subjects with mental handicap and epilepsy. They compared 150 subjects with mental handicap and epilepsy with a similar number of subjects with mental handicap but no epilepsy, using the Profile of Abilities and Adjustment Schedule for maladaptive behaviour. They found that while over half the total study population showed some severe maladaptive behaviour, the problems in the epilepsy population were slightly more severe. The difference was not statistically significant (1991a).

In summary therefore, while there is little doubt that patients with LD and epilepsy have high rates of psychiatric co-morbidity (as high as 90% in some series), it is not entirely clear if an increased burden of psychiatric disorder attributable to epilepsy exists in this population.

3.3.2. Patterns of Psychiatric Co-Morbidity in Subjects with LD and Epilepsy

Attempts to classify psychiatric disorders in children with LD and/or active epilepsy have been few. Hyperactivity, rage, antisocial behaviour and schizophrenia-like psychosis have all been reported, particularly in connection with temporal lobe epilepsy (Rutter, 1970; Caplan, 1991).

In Lund's series (1985b), the author using previously modified (for mental retardation) versions of Feighner's criteria and DSM III criteria identified an overall prevalence of 27.1%, which is lower than most other studies. When patterns of psychopathology were compared, apart from a generic behaviour disorder category (10.9%), psychoses of uncertain type (5%), dementia and early childhood autism (3.6% each), neurosis (2%), schizophrenia (1.3%) and affective disorder (1.7%) were all identified. No cases of alcohol or drug abuse were identified in this study.

In Deb and Hunter's series (1991a,b,c) mild to moderately impaired subjects with good communication skills who were positive on the PAA schedule for psychiatric illness were interviewed using the Present State Examination interview schedule, while those with severe mental retardation were observed and information collected from their medical notes and from the carers. Psychiatric diagnosis was made based on DSM-III-R criteria (Deb & Hunter, 1991b). Psychiatric illness was diagnosed in almost one-quarter of the population studied, but was commoner in the non-epilepsy group than in the epilepsy group, the difference being statistically significant.

There were however, distinct patterns of psychiatric disorder reported in the epilepsy group. For example, changeable mood – although this did not reach statistical significance. Other differences of interest were the relative absence of bipolar disorder in the epilepsy group and the relative over-representation of non-affective psychoses in the epilepsy group, for which there is epidemiological evidence (Jalava & Sillanpaa, 1998). There also were differences between community and hospital populations – behaviour such as irritability progressing to aggression being more commonly reported in the hospital population.

They also compared mild to moderately handicapped people with epilepsy and without, using the Standardised Assessment of Personality and the T-L Personality Behaviour Inventory. They found that 26% of the entire cohort had an abnormal personality score according to the SAP schedule, and a significant proportion of these were personality disorders. The vast majority of those with high SAP scores were in-patients. However, there were no statistically significant differences between epilepsy and non-epilepsy groups (Deb & Hunter, 1991c).

In a representative population-based study Steffenberg et al. (1996) identified 98 children with MR and active epilepsy, from among 48,873 children living in Goteborg (Sweden), through multiple search procedures. The children were between 8–16 years of age, and of 98 identified, five had died and three declined to be examined. An experienced child neuropsychiatrist examined 90 children by interviewing the mother or principal caregiver using the Handicap, Behaviour and Skills Schedule, each interview lasting between 60–150 minutes. Further, each child was observed for 30 minutes. Other scales used in this study included the Childhood

Autism Rating Scale and Autistic Behaviour Checklist, Asperger Syndrome Diagnostic Checklist, and Global/Social and Occupational Function Assessment Scales (GAFS & SOFAS). In addition to co-morbid psychiatric disorder, cerebral palsy, visual and hearing deficits and self-injurious behaviour were all rated for.

Fifty three (57%) of 90 children received at least one psychiatric diagnosis. Autistic Disorder was the most common diagnosis (24/90); followed by Autistic Like Condition (10/90); Attention Deficit Hyperactivity Disorder (6/90); Asperger Syndrome, Autistic Traits and Overanxious Disorder (3/90 each); stereotypy/habit disorder, elective mutism, conduct disorder, chronic motor tic disorder (1/90 each). 28(31%) of children in this sample had self injurious behaviour. Interestingly, a further 30 of these 90 children, many with profound mental retardation and severe communication difficulties, were classified as "uncategorisable conditions and dementias", and only 5 of 90 subjects were declared normal. Medical syndromes (excluding epilepsy syndromes) were observed in 11 subjects, 8 of who were in the Autistic Disorder (AD) group, none in the Autistic Like Condition (ALC) group and 3 in the non-AD/ALC group, this difference being statistically significant ($p<0.001$). Psychiatric co-morbidity was generally high, with a number of patients meeting more than one diagnosis, although in some conditions such as ALC, Asperger and Autistic Traits, diagnostic criteria such as DSM were not used. This study also showed that AD in particular, was associated significantly with temporal lobe epilepsy. Interestingly too, the percentages of psychiatric disorder (AD for e.g.) were not significantly different between mild mental retardation (MMR) and severe mental retardation (SMR) groups, which is different from other series (Wing, 1993).

The authors of this study have argued elsewhere (Steffenberg U & Steffenberg S, 1999) that that the low prevalence of psychiatric disorder (57%) may be down to the very large proportion (almost a third) classified as "unrecognisable condition and dementia". Further, the finding that AD was by far the commonest psychiatric disorder, while not entirely commonplace, is supported by the strong associations between autism and epilepsy reported elsewhere (Olsson et al., 1988). The use of specific instruments targeted towards the identification of AD in this study, which has not been done in other studies, may explain this finding at least in part.

3.3.3. Neuropsychiatric epidemiology at the interface between epilepsy and LD; summary of current studies

As reviewed herein, the evidence about the relative frequency of psychiatric disorder in learning disabled populations with epilepsy is both confusing and contradictory. Further, there are a number of specific issues that have not been addressed before.

First, what is available in the main is prevalence data from hospital, institution and a few community-based studies. However, while data of this nature inform about the public health burden of such co-morbidity, it do not help in making scientific inferences about important factors such as causality and risk. Good analytical epidemiology is required for this, and can only be achieved through well-designed and conducted cohort and case control studies, based on the population.

Second, although specific behaviour patterns have been observed, few studies have compared generic and epilepsy specific behaviours in these populations. The

study of generic psychopathology is important for purposes of comparing the learning disabled population with co-morbid epilepsy, with learning disabled populations without epilepsy, and indeed non-learning disabled populations in the community. On the other hand, as demonstrated by Steffenberg et al. (1996), the use of instruments that can assess for specific behaviours such as the Autistic Spectrum Disorders, aggression, psychosis etc., is likely to yield rich data, and provide greater understanding about the nature and mechanisms of psychopathology at this interface. Apart from being of heuristic interest, this data has practical implications as well, with psychiatric and psychological interventions for example being behaviour specific to a very great extent.

Third, it is important to note that a number of the studies have used instruments that have not been specifically developed either for epilepsy or for LD. In recent times various influential groups have been working towards building consensus in the choice of outcome measures (Kerr & Espie, 1997 for e.g.). Appropriate measures include – datasets for aetiology and seizure type, seizure frequency, behaviour, social interaction, patient independence, contact and participation, general well being and quality of life including carer's quality of life. It has been suggested that a range of standard outcome measures be used in researching this interface, and that these should be sensitive to change, include information on individual characteristics, and allow for variables such as treatment compliance and environmental confounders. In addition, there may be room for new technologies such as direct observation through computer systems and video recordings.

Fourth, there is considerable debate about the choice of psychopathology measure. In a recent review and position statement Espie et al. (1997) have short-listed several measures, and compared their relative attributes. The Psychopathology Instrument for Mentally Retarded Adults (Senatore, 1985), the PAS-ADD (Moss et al, 1993), Aberrant Behaviour Checklist (Aman et al., 1985)), Psychosocial Behaviour Scale (Espie et al., 1988), Adaptive Behaviour Scales- Part Two (Guess et al., 1990), Attention Deficit and Hyperactivity Questionnaire (Boudreault et al., 1988), Society for the Study of Behavioural Phenotypes (SSBP)- Postal Questionnaire (O' Brein, 1996) are all instruments that have been used fairly extensively in this area. The precise choice of instrument(s) will have to be made following a careful review of the study objectives, balanced against the relative abilities and characteristics of these instruments, and pragmatic concerns. In addition to this list above, there may be some justification in including a scale for autistic behaviours following on from Steffenberg's influential paper (1996), and a structured carer report for psychopathology such as the Neuropsychiatric Inventory (Cummings et al., 1994). Such structured carer-rated information, which has not been ascertained in many previous studies, may be potentially valuable in developing interventions for LD & epilepsy.

Fifth, it has been pointed out that LD can be a state dependent phenomenon, and thus potentially reversible (Besag, 2001). State dependent LD can broadly be of two types – drug- and epilepsy- induced. Drugs like phenobarbitone, primidone, benzodiazepines and sodium valproate are known to cause cognitive deficits (the latter producing an encephalopathy) resulting in state dependent LD. On the other hand, epilepsy induced state dependant LD may result from the ictal effects of sub-

clinical seizures, focal discharges, post-ictal states, non-convulsive status and the syndrome of Electrical Status Epilepticus in Sleep (ESES). While state dependent LD may only form a small proportion of LD cases, its reversible nature dictates that it is examined for and carefully excluded in LD studies including population-based studies. Screening instruments sensitive to these phenomena thus need to be developed, and incorporated into the package of diagnostic measures used.

Finally, in an ideal world, cohorts/registries of LD should be established prospectively, and include each patient who receives LD diagnosis. Prospective follow-up of such a cohort for co-morbid epilepsy and/or psychopathology, and nested case-control studies for risk factors, aetiology, biological and clinical correlates, quality of life, prognostic indicators, treatment response and other measures of outcome would reveal valuable epidemiologically valid information at this interface. The use of standard outcome measures as outlined previously would of course, greatly aid the research process. However, this approach is tedious, expensive and long drawn out. And not surprisingly the gamut of research thus far has come from Northern Europe, where health care systems include the establishment and maintenance of registries.

In conclusion, neuropsychiatric epidemiology at the interface between LD and epilepsy is poorly researched. A better understanding about this interface, would no doubt lead to focussed interventions in the community and resultant improvements in health care for learning disabled populations with co-morbid epilepsy (Beber et al., 1999 for e.g.). The development of consensus (Kerr & Espie, 1997); the identification of reliable and valid outcome measures and development priorities (Espie et al., 1997); detailed studies based in the community (Steffenberg et al., 1996); as well as

recent comprehensive reviews of LD and epilepsy (Sillanpaa et al., 1999), have set the stage for high quality research efforts at this interface that must follow in the years to come.

3.4. Neuropsychiatric Epidemiology in Adult Non-Learning Disabled Populations with Epilepsy

3.4.1. A Review of Large Hospital and Institution-Based Studies

A number of studies in this area have been hospital/institution-based. While the strong selection bias in these studies makes the extrapolation of their findings difficult to the majority of patients with epilepsy, who live in the community, the contribution of these studies to the current understanding of psychopathology in epilepsy has been invaluable and they are briefly reviewed here.

Currie et al. (1971) surveyed 666 patients recorded to have features of temporal lobe epilepsy in the hospital diagnostic index and the records of the neurology, neurosurgery and EEG departments. They found 375(56%) to be normal, 127(19%) to be anxious, 71(11%) to be depressed, 47(7%) to be aggressive, 41(6%) to be obsessive and 38(6%) to have a severe disturbance of affect.

Smith et al. (1986) studied 622 patients in a nation-wide co-operative study spanning 10 Veterans Administration Medical centres in the USA, using a battery of neuropsychological testing procedures. The majority of patients were not on anticonvulsant drugs at the time of initial testing, and the few who were, had sub-

therapeutic levels on measurement. They found that patients with epilepsy scored significantly and consistently below the level of the 74 control subjects on all but three behavioural measures. Differences reaching statistical significance were found on tests of motor function (Finger Tapping, Pegboard, Colour Naming), cognitive-attention (Digit Symbol, Discrimination Reaction Time, Word Fluency), and subtests of the Profile of Mood States (tension, depression, vigour and confusion). These they felt provided a profile of behavioural characteristics of unmedicated patients with epilepsy.

Gureje (1991) evaluated 204 unselected patients with epilepsy attending a neurological clinic using the Clinical Interview Schedule (Goldberg et al., 1970). 37% emerged as psychiatric cases; of these 53% had a neurosis, 29% had a psychosis, and 7% were diagnosed to have a personality disorder.

Mendez et al. (1993) conducted a retrospective investigation of neurology clinic attenders. They found that interictal schizophrenic disorders occurred in 149(9.25%) of 1,611 patients with epilepsy as compared to only 23(1.06%) of 2,167 patients with migraine. They went on in the latter part of the study to compare 62 epilepsy and schizophrenia patients with 62 patients who had epilepsy alone on 6 seizure variables and 62 patients with schizophrenia alone on 10 psychosis variables.

The epilepsy and schizophrenia group was found to have a later age of onset of epilepsy with more complex partial seizures, more patients with auras and fewer patients with generalised epilepsy. Except for increased suicidal behaviour, patients with epilepsy did not differ from controls on psychosis variables; however psychotic symptoms often emerged with increased seizure activity. They felt that the data

supported a distinct association of schizophrenic disorders with epilepsy, particularly with seizures emanating from the temporal limbic system.

Manchanda et al. (1996) studied 300 consecutive patients with refractive to treatment, admitted to for evaluation of their candidature for epilepsy surgery over a six year period. Of these 231 had a temporal lobe focus, 43 had a non-temporal lobe focus and 26 generalised and multifocal seizure onset.142 (47.3%) emerged as psychiatric cases based on DSM III-R criteria. A principal axis I diagnosis was made in 88(29.3) patients. Anxiety disorders (10.7%) and Schizophrenia (4.3%) were the most common axis I diagnosis. Dependent and avoidant personality traits were frequent (18%) although patients rarely fulfilled criteria for a personality disorder.

3.4.2. Population-based Studies

One of the earliest investigations to be carried out was that of Pond and Bidwell (1960), who surveyed patients from 14 general practices in the South East of England. They found that 29% of 245 patients had psychological disorders of sufficient severity to seek treatment, i.e., conspicuous morbidity. The main criticism levelled against this study is its use of a social worker rather than a trained mental health professional, and a lack of standardised techniques to assess patients with epilepsy for psychiatric co-morbidity. The strength of this study however lies in its recognising, four decades earlier, the importance of an epidemiological approach.

Gudmundsson (1966) personally surveyed 987 patients with epilepsy living in Iceland and reported that 512(52%) had personality changes of various kinds. Of

these 271(27.5%) were described as ixoid, 73(7.4%) as ixothymic and 168(17.0%) as neurotic. More men were ixoid and more women neurotic. While Gudmundsson, unlike Pond, personally examined every subject, the method of measurement, clinical terminology and classification used have few parallels today, and no attempts were made to reduce bias. However, the high proportion of subjects with behavioural changes in this community-based population is striking and worthy of note.

Edeh and Toone (1987) conducted a survey in general practises in South London. They interviewed 88 adult patients with epilepsy drawn from general practises in the area, using the Clinical Interview Schedule, and reported that 48% emerged as psychiatric cases. They also found that while patients with TLE and Focal non-TLE did not differ in terms of psychiatric morbidity, both groups were significantly more impaired than patients with primary generalised epilepsy. The techniques of ascertainment used in this study are commendable. Subjects with epilepsy underwent both CT scans and EEG tests, in confirmation of their diagnosis. The study also used a validated instrument for common mental disorder, the CIS-R. In criticism, however, it must be said that the study failed to examine matched population-based controls, psychopathology specific to epilepsy was not examined. And while cases with psychosis were identified, no validated diagnostic instrument for psychosis was administered, the CIS-R being a validated instrument for common mental disorder alone.

Cockerell et al. (1996) conducted a nation-wide survey of acute psychological disorders (APD) in patients with epilepsy using the British Neurological Surveillance Unit. 64 incident cases were ascertained over a period of one year. Thirty-one were

considered to have APD due to ictal/post-ictal activity and 33 were inter-ictal. In 30% of cases the APD was reported by the referring physician to be secondary to an Anti Epileptic Drug. The drugs most commonly implicated were carbamazepine, lamotrigine and vigabatrin. The broad psychiatric categories diagnosed included Delirium (25%), Schizophreniform (31%), Affective (30%), Delusional (5%) and other disorders (9%). The findings of this study are of interest as it gives us crude incidence figures of acute psychiatric disorder in epilepsy and highlights the importance of anti-epileptic drugs in precipitating co-morbid psychiatric illness in epilepsy. However, as the study used a reporting system, rather than a population based cohort, the results cannot be used to generate population-based incidence figures, or be generalised.

Jacoby et al. (1996) retrospectively examined the clinical course of epilepsy in subjects with epilepsy, and the associations between seizure severity, psychological morbidity and disablement. Subjects were drawn from the records of 31 general practitioners in the UK, and 71% of all subjects responded, when contacted. Twelve percent of the total sample had a past psychiatric history. Of the 696 respondents 46% reported being in a 2-year remission, and 51% reported being seizure free in the past year. Overall 25% of subjects were classified by the Hospital Anxiety Scale as being anxious and 9% as being depressed (total scores >11 on the relevant subscales). A clear relationship was observed between the level of current seizure activity and the subject's psychological well being. Current level of seizure activity also influenced subjects' perceptions about the impact of epilepsy and the treatment on their daily lives. Seizure severity also influenced life fulfilment but not material fulfilment. Both anxiety and depression scores correlated with current seizure activity ($p<0.001$). In

the multivariate analysis, current seizure activity was the only clinical variable that explained the most variation in psychosocial functioning. Other variables such as age of onset and duration of epilepsy were also important in explaining variation in depression scores. Age was also important in explaining the variation in the stigma scales.

In a further paper arising from the aforementioned study, Baker et al. (1996) examined the relationship between clinical, demographic and psychosocial variables. Each individual who took part in the study completed the Liverpool seizure severity scale, impact of epilepsy scale, adverse drug events profile, hospital anxiety and depression scale, sigma scale (for the assessment of perceived stigma) and information about seizure variables (frequency, age of onset, duration etc.). Both anxiety and depression on the HADS were good predictors of impact in the multivariate analysis. Seizure frequency was a significant predictor of scores on the anxiety and depression scales and on the impact and stigma scales. The amount of variance explained by seizure frequency was negligible in comparison to that explained by the psychosocial variables. However, when patients who had seizures in the past 12 months were examined, seizure severity became an important predictor of depression, anxiety and impact scores.

Jalava and Sillanpaa (1996) examined a prospective population-based cohort (mean follow-up of 35 years) of patients with epilepsy since childhood, for co-morbid somatic, psychosomatic and psychiatric disorders. The main advantage of this study was that patients had been included in the register as children, and thus naturalistic follow up data was available. In comparison with random controls, patients with

epilepsy had a four-fold risk of psychiatric disorders or combinations of somatic, psychosomatic/psychiatric disorders. Thus patients with childhood onset epilepsy demonstrated a higher risk for psychiatric/psychosomatic disorders and this appeared to be related to epilepsy and not AED administration.

This is perhaps the only cohort study of psychiatric co-morbidity in epilepsy and the findings have great relevance. The results clearly indicate that subjects with epilepsy are at higher risk of developing co-morbid psychiatric illness, when compared to population-based controls, and indicate the need for greater provision for psychiatric treatment in primary care settings for epilepsy. However, as individual cases were not ascertained in any systematic way, it is possible that the findings do not represent the true extent of co-morbidity, subtle nevertheless disabling forms of psychopathology, or those not requiring medical attention or admission, being missed. This is of relevance, as subtle forms of psychopathology that often do not meet conventional diagnostic criteria, may be over-represented in epilepsy.

Bredkjaer et al. (1998) conducted a record linkage study in Denmark between a sample of people with epilepsy from the National Patient Register and the Danish Psychiatric Register. They found that the incidence of non-organic non-affective psychoses including personality disorders that were broadly within the Schizophrenia Spectrum, was significantly increased for both men and women with epilepsy, even after excluding all people diagnosed as suffering from a learning disability or substance misuse. The standardised incidence ratio was significantly increased for the entire schizophrenia spectrum ($p<10-8$), non-affective psychosis ($p<10-8$) and schizophrenia alone ($p<0.0001$).

In the absence of long-term prospective data, this study based on national registers provides evidence that, disorders in the schizophrenia spectrum, are clearly over-represented in epilepsy. The study enabled the calculation of more sophisticated epidemiological indices, such as standardised incidence ratio that have not been estimated in previous studies. However, the methodological limitations of reliance upon a case-register, i.e., the lack of standardisation of ascertainment methods, both for epilepsy and psychoses, and the exclusion of more subtle cases, or those not requiring admission, do apply here.

Stefansson et al. (1998) conducted a case-control study comparing the prevalence of non-organic psychiatric disorders among patients with epilepsy, and controls with other somatic diseases, both groups being of normal intelligence. The two groups were drawn from a disability register of the State Social Security Institute in Iceland. 241 index cases meeting inclusion criteria were identified in this way and the ratio between subject (epilepsy) and control (somatic illness) cases was 1:2. Psychiatric diagnosis was present among 35% of cases as compared to 30% of controls, the difference not being statistically significant. Psychiatric disorders were however significantly more common in men with epilepsy than women, the difference being due to a significantly higher rate of psychosis, particularly schizophrenia or paranoid states among men.

O'Donoghue et al (1999) examined 169 subjects with epilepsy in two large general practices in the UK. The Hospital Anxiety and Depression Scale was used to diagnose anxiety and depression and the Subjective Handicap in Epilepsy scale to assess disablement. Seizure frequency was assessed but not seizure severity. An

association was established between seizure frequency and subjective handicap; the less frequent the seizures, the lower the level of subjective handicap. About half of all patients with more than one seizure per month were severely handicapped. A comparison between more and less than one seizure per month was significant on four of the scales.

Thirty four percent of subjects had consulted their GP at some time for psychiatric symptoms, depression (23%), anxiety (6.5%) and overdose (6%) being the commonest symptoms. The prevalence of recorded psychiatric symptoms in the 2 years before the study, in patients with active epilepsy was 20%, in those with remitted epilepsy on treatment was 18%, and in the remitted off treatment group the prevalence was 17%. About one-half of patient having more than one seizure per month and one-fifth of those in remission were classified as having definite anxiety or definite depression using the HADS. Table-1 summarises the key epidemiological studies of neuropsychiatric co-morbidity in epilepsy.

Table 1. Important Epidemiological Studies of Neuropsychiatric Co-Morbidity in Epilepsy.

Year	Investigators/Country	Results	Comments
1960	Pond and Bidwell (UK)	29% of 245 patients had significant morbidity	Study in 14 general practices Conducted by Psychiatric Social Worker Instruments not standardized
1966			Personal survey by expert

	Gudmundsson (Iceland)	512(52%) of 987 patients had personality changes	Instruments and diagnosis not standardized
1987	Edeh and Toone (UK)	48% of 88 patients emerged as cases	Primary care-based
			Sophisticated case ascertainment
			Standard instruments but not epilepsy specific
1996	Cockerell et al. (UK)	64 incident cases of acute psychological disorder on AED institution	Nation wide survey
			Relied on reporting system
			Crude data on incidence - cannot be generalised
1996	Jacoby et al. (UK)	Large community-based study – 696 subjects	Ascertainment of epilepsy based on GP records
		25% classified as anxious and 9% as depressed	HADS used with cut-off scores of 11 to identify psychiatric caseness
		Seizure severity and age at epilepsy onset were significant predictors of depression, stigma and marital status.	Large sample, sophisticated statistical techniques
			However instruments employed including HADS have not been validated in epilepsy populations

		Examined the relationship between seizure severity and psychosocial variables	Same large sample as Jacoby et al. above: criticisms about ascertainment as above
		Both HADS anxiety and depression- good predictors of impact	Measurement of psychosocial variables by widely used instruments- not necessarily epilepsy specific
1996	Baker et al. (UK)	Seizure frequency significant predictor of HADS scores and impact and stigma scales	Absence of gold-standard measures except seizure severity
		Psychosocial variables explain greatest proportion of variance	HADS not diagnostic of psychiatric disorder although it is a validated measure of psychological morbidity
		Patients with seizures in the past 12 months: seizure severity important predictor of psychosocial variables.	

1996	Jalava and Sillanpaa (Finland)	patients with epilepsy- four-fold risk of somatic, psychosomatic/ psychiatric disorder in combination compared to population-based controls	Prospective cohort study with 35 year follow-up (only cohort study to date)
		Results related to epilepsy and not AED administration	Results clearly indicate that subjects with epilepsy are at higher risk of developing co-morbid psychiatric illness
1998	Bredjkaer et al. (Denmark)	Incidence of Schizophrenia Spectrum psychoses significantly increased for both men and women with epilepsy	Record linkage study between a sample of people with epilepsy from the National Patient Register and the Danish Psychiatric Register
		Standardised incidence ratio for the entire schizophrenia spectrum (p<10-8), non-affective psychosis (p<10-8) and schizophrenia alone (p<0.0001).	Enabled the calculation of sophisticated epidemiological indices not estimated in previous studies

1998	Stefansson et al. (Iceland)	Psychiatric diagnosis in 35% of 241 epilepsy cases as compared to 30% of controls, the difference not being statistically significant	Patients with epilepsy, and controls with other somatic diseases, both groups being of normal intelligence drawn from a disability register of the State Social Security Institute
		Significantly higher rate of schizophrenia among men.	
1999	O'Donoghue et al. (UK)	Between one-third and one-half of all patients diagnosed to be 'cases' on HADS	Good ascertainment: screening and examination by specialists
		One third of patients with active epilepsy severely handicapped by their condition	Measurement of seizure severity not well standardised
		Association between seizure severity, frequency and subjective handicap	Associations between seizure severity/frequency, psychological morbidity and subjective handicap were not studied
		Psychological morbidity	Lack of sophistication in statistical methodology

		poorly recognised by GP's	HADS used with cut-off scores of 10/11 for definite and 7/8 for borderline
			SF-36 good generic measure of disablement used here

3.4.3. Summary of Findings: Neuropsychiatric Epidemiology of Epilepsy

Psychiatric disorders are common in epilepsy, and encompass the spectrum of conditions from those that are a direct consequence of epileptogenic activity, to others that are merely co-morbid.

There is considerable evidence from epidemiological research to suggest that the psychoses are greatly over-represented in epilepsy; the evidence for an over-representation of other psychiatric disorders is less compelling.

While hospital-based data indicates the presence of epilepsy specific psychopathology, this has never been examined in the epidemiological setting. Further, instruments such as the NBI that are supposedly sensitive to epilepsy specific psychopathology have not been validated in this setting.

Systematic population-based research using reliable methods of ascertainment, and controls matched for age, sex, disability and ethnicity, based on the ILAE classification of neuropsychiatric disorders in epilepsy, incorporating instruments of

psychiatric research as well as scales for seizure severity and disablement need to be conducted in the future.

3.4.4. Classification of Psychiatric Co-morbidity in Epilepsy

3.4.4.1. Why a Separate Classification?

The primary reason to develop a system of classification is to ensure that specialists around the world have no difficulty in communicating scientifically with one another. This is perhaps more important in psychiatry, a speciality that relies on clear and concise descriptions in the absence of diagnostic tests. A reliable system of classification that can be applied across the board is essential for clinical and scientific progress.

The classification of psychiatric disorders in epilepsy has always been controversial. There are two main schools of thought. First is that the existing systems of classification in psychiatry, the ICD, now in its tenth edition and the DSM, in its fourth edition, have made adequate provision for "organic" conditions like epilepsy, and further sub-systems of classification would only add to their complexity. Second, most often voiced by neuropsychiatrists with an interest in epilepsy, that the existing systems of classification are hopelessly inadequate as far as neurological disorders in general and epilepsy are specifically concerned.

The question "are psychiatric disorders commoner in epilepsy?" has not been answered convincingly to date. While there seems little room to doubt that the

psychoses are over-represented in epilepsy, perhaps ten times as common as in the general population, the evidence with regard to common mental disorders is far from clear. This is largely due to the paucity of epidemiological studies of psychiatric co-morbidity in epilepsy (Krishnamoorthy, 2001; 2002).

One criticism that has been put forth about the studies that have been done is that the instruments used are most often generic to mental disorder rather than specific to epilepsy. Yet, in contrast to this, a number of hospital/clinic-based studies have drawn attention to psychopathology that is specific to epilepsy including personality change, psychoses, affective disorder, and phobic-anxiety disorders (Trimble, 1991; Blumer, 2000).

Unfortunately, instruments such as the Neurobehavioral Inventory for Epilepsy (modified version of the Bear–Fedio scale), developed specifically for epilepsy (Blumer, 1995), have not been subject to rigorous psychometric testing and have failed to gain widespread acceptance. The failure to consistently demonstrate an over-representation of psychiatric disorders in epilepsy when compared to some other chronic illness groups, in several studies, may thus be due to the use of inappropriate instruments that are not sensitive to epilepsy related neuropsychiatric disorders, rather than a difference in prevalence (Krishnamoorthy, 2001; 2002).

Were we to accept that neuropsychiatric disorders specific to epilepsy exist, the reasons to develop a system of classification become immediately obvious. Indeed it could be argued that such a classification framework is necessary for any

prospectively designed investigations of epilepsy specific disorders in community-based studies.

3.4.4.2. What are the Neuropsychiatric Disorders Specific to Epilepsy, and How could they be Classified?

The neuropsychiatric disorders specific to epilepsy represent the gamut of neuropsychiatry. Included are the so-called organic mental disorders such as post-ictal confusional states and complex partial status with psychopathological manifestations; personality changes (the Gastaut–Geschwind syndrome of temporal lobe epilepsy, and the labile personality of Juvenile Myoclonic Epilepsy); a spectrum of psychoses with varying intensity, features and manifestations depending on the temporal relationship with seizure(s) (Trimble, 1991); and a spectrum of neuroses with predominantly affective features (Blumer, 2000). These disorders are also inexorably linked to their relationship with the seizure(s) per se (pre-ictal, post-ictal, inter-ictal and perhaps peri-ictal); their relationship to the EEG, (for example, Forced Normalization of Landolt and alternative psychosis of Tellenbach) (Krishnamoorthy & Trimble, 1999); and their relationship to anti-epileptic drug (AED) therapy (the AED induced neuropsychiatric disorders) (Trimble, 1998). Thus any classificatory system will need to take all these factors into consideration.

Further, it is important to acknowledge that patients with epilepsy like all patients with chronic medical illnesses have greater vulnerability to co-morbid psychiatric disorders that match existing descriptions in ICD-10 and DSM-IV. It would serve little purpose to try and re-classify these disorders when associated with

epilepsy. The judgement about whether to record the illness in the given patient as a co-morbid disorder or as an epilepsy specific disorder would be best left to the clinician dealing with that individual case. It also goes without saying that such a classificatory system should link closely with the ILAE Classification of Epilepsies and Epileptic Syndromes.

The inclusion of non-epileptic attack disorder (NEAD) in such a classification is rather more controversial, as there is a growing understanding that NEAD is, in a number of subjects, the manifestation of a much wider spectrum of psychopathology than that specific to epilepsy (Brown & Trimble, 2000).

There is little doubt that classifications grounded in aetiology and pathophysiology are an ideal that must be aspired for in the long term. However, our understanding of causation and its mechanisms in psychiatry, even the neuropsychiatry of epilepsy, is fairly rudimentary. And much ground needs to be covered before we can move with any certainty towards such etiological models. Further, etiological systems of classification require specialised knowledge and access to supportive investigative techniques. Both of these are unavailable in a number of settings, particularly in the developing world. Classificatory systems that aim to be culture-free and acceptable across the board would do well to adopt a descriptive approach based on a good history and clear clinical descriptions that mirrors good clinical practice around the world, and makes few demands in terms of specialist expertise or investigation (Krishnamoorthy, 2000a).

3.4.4.3. Towards a System of Classification – The ILAE Proposal.

While there are different ways of classifying mental states, the clinical approach of observing patients over a prolonged period of time is by far the most important. Further, while there is good empirical evidence to suggest that the psychiatric disorders of epilepsy are clinically distinct, they do not find a place in the current classificatory systems in psychiatry, such as ICD-10 and DSM-IV. Besides, operational rules that exist ensure that they are subsumed within categories (organic mental disorder for example), in a way that may neither be appropriate nor accurate. As these disorders are phenomenologically distinct, and may respond to specific therapeutic measures (IDD: Blumer, 2000 for example), this is clearly unsatisfactory. Modern efforts must be directed at developing a more comprehensive and acceptable system of classification, for psychiatric disorders in epilepsy. With this in mind the First Psychobiology Commission of the International League Against Epilepsy (ILAE) established a sub-commission to work towards the development of a classificatory system. The work of this sub-commission is contained in a report submitted to the ILAE with a view to publication in Epilepsia, which was the result of extensive deliberations, and is reproduced herein with the kind permission of the commission chair, Prof. MR Trimble.

3.4.4.4. The Problem of Co-morbidity

Patients with epilepsy, similar to patients with other chronic medical illness, have a significant liability to co-morbid psychiatric disorders (Krishnamoorthy, 2002a). These co-morbid disorders do not usually have specific distinguishing features, which

separate them from those seen in other medical illnesses or those seen in the community.

Included here are anxiety and phobic disorders, minor/major depression, obsessive–compulsive disorder etc. In addition, patients with epilepsy also suffer from co-morbid major psychiatric disorders such as bipolar-affective disorder and undifferentiated forms of schizophrenia. Co-morbid mental disorders therefore should be classified using conventional criteria.

Suggestion: Ignore the presence of epilepsy in making the diagnosis to prevent the imposition of the "Organic" category in these conventional psychiatric classifications.

3.4.4.5. Psychopathology as a Presenting Feature of Epileptic Seizures

Psychiatric symptoms are often a feature of the seizure itself. Auras of simple partial seizures include psychiatric symptoms like anxiety and panic, hallucinations in various modalities and even transient abnormal beliefs. Abnormal (sometimes bizarre) behaviour can also characterise partial seizures arising from the frontal and temporal lobes that often do not generalise. Sub-clinical seizure activity (often non-convulsive status) can also present with catatonic features, and other neuropsychiatric manifestations like apathy and aggression (Trimble, 1991).

Well-defined ictal states are included here:

- Complex partial seizure status: presents with impaired awareness
- Simple partial seizure status (aura continua): presents with intact awareness
- Absence status (spike-wave stupor): presents with a stuporous state and at times with minor myoclonic manifestations

Specify: Relationship to EEG as described later in this paper

3.4.4.6. Psychiatric Disorders with Ictal Associations that are Specific to Epilepsy

There are disorders that are seen specifically in patients with epilepsy. These have distinct clinical descriptions and may respond to specific forms of treatment. These can be broadly divided into the following categories:

3.4.4.6.1. Cognitive Dysfunction

Patients with epilepsy refractory to treatment suffer from cognitive dysfunction either due to the epilepsy itself, due to the complications of epilepsy, or due to anti-epileptic drugs. Impairments include difficulties with memory, language, executive functions, visuospatial ability and sensorimotor/perceptual functions. These may be general or specific (Perrine & Kiolbasa, 1999).

Some specific neurocognitive deficits such as the Landau–Kleffner syndrome, which can be associated with specific EEG changes such as Electrical Status

Epilepticus of Slow Wave Sleep (ESES), or Continuous Spike and Wave in Slow Wave Sleep (CSWS) to be included here (Besag, 2001).

3.4.4.6.2. Psychoses of Epilepsy

2.1. Inter-ictal psychosis of epilepsy: This is a paranoid psychosis with strong affective components but not affective flattening usually. Features may include command hallucinations, third person auditory hallucinations and other first rank symptoms. There is a preoccupation with religious themes. Personality and affect tend to be well preserved unlike in other forms of schizophrenic psychosis. Psychotic features are usually independent of seizures, although they may become manifest as seizure freedom lessens (Trimble, 1991).
Include: Schizophrenia-like psychosis of epilepsy
Exclude: Cases fulfilling criteria for undifferentiated or hebephrenic schizophrenia.

2.2. Alternative psychosis: The patient alternates between periods of clinically manifest seizures and normal behaviour, and other periods of seizure freedom accompanied by a behavioural disturbance. The behavioural disturbance is often accompanied by paradoxical normalisation of the EEG (forced normalisation) (Landolt, 1953; 1958). The behavioural disturbance is polymorphic with paranoid and affective features. The diagnosis of Alternative Psychosis (Tellenbach, 1961) should be made in the absence of the EEG. If EEG confirmation is available, the diagnosis should be qualified further as "with forced normalization of the EEG".
Include: Forced Normalization/Paradoxical Normalization (Wolf, 1991). Include also cases with relative normalization as defined by Krishnamoorthy and Trimble (1999).

Exclude: Continuing inter-ictal psychosis or post-ictal psychosis (recent cluster of seizures); non-convulsive status with psychiatric manifestations.

2.3. Post-Ictal psychosis: Follows clusters of seizures (rarely single seizures) usually after a 24–48 hour period of relative calm (the lucid interval). These episodes can last from a few days to several weeks, but usually subside in one/two weeks. Confusion and amnesia may be present. The content of thought is paranoid and visual and auditory hallucinations may be present. Manifestations are often polymorphic with affective features and a strong religious theme (Trimble, 1991).

Include: Cases with a clear history of a cluster of seizures or an isolated single seizure (in a patient who has been seizure free). The first manifestation of abnormal behaviour should occur within a seven-day period from the last seizure (Logsdail & Toone, 1988).

Exclude: Post-ictal confusion; non-convulsive status with psychiatric manifestations.

3.4.4.4.5. Affective-Somatoform (dysphoric) Disorders of Epilepsy

Intermittent affective-somatoform symptoms are frequently present in chronic epilepsy. They present in a pleomorphic pattern and include eight symptoms: irritability, depressive moods, anergia, insomnia, atypical pains, anxiety, and euphoric moods. They occur at various intervals and tend to last from hours to two/three days, although they might on occasion last longer. Some of the symptoms may be present continually at a baseline from which intermittent fluctuations occur. The presence of at least three symptoms generally coincides with significant disability (Blumer, 2000).

The same affective-somatoform symptoms occur during the prodromal and post-ictal phases and need to be coded as such if they are of clinical significance.

3.4.4.4.5.1. *Interictal dysphoric disorder*: Intermittent dysphoric symptoms (at least three of the above) are present, each to a troublesome degree. In women the disorder is manifest (or accentuated) in the pre-menstrual phase.

3.4.4.4.5.2. *Prodromal dysphoric disorder*: Irritability or other dysphoric symptoms may precede a seizure by hours or days and cause significant impairment.

3.4.4.4.5.3. *Post-ictal dysphoric disorder*: Symptoms of anergia or headaches as well as depressed mood, irritability or anxiety may develop after a seizure and be prolonged or exceptionally severe.

3.4.4.4.5.4. *Alternative affective-somatoform syndromes*: Depression, anxiety, depersonalisation, derealisation, and even non-epileptic seizures have been reported as presenting manifestations of forced normalization (Wolf, 1991). These may be diagnosed in the absence of an EEG as described previously, and in the face of EEG evidence coded as "with forced normalization of EEG".
Include: Brief lasting but disabling changes in affect. Exclude: Patients fulfilling ICD-10 and DSM-IV criteria for major depression, dysthymia and cyclothymia.

3.4.4.4.6. Personality disorders

Patients with chronic epilepsy may show distinct personality changes that tend to be subtle. Three types are recognised:

(1) A deepening of emotionality with serious, highly ethical and spiritual demeanour (Geschwind, 1977).

(2) A tendency to be particularly detailed, orderly and persistent in speech and action viz. viscosity (Blumer, 1995).

(3) A labile affect with suggestibility and immaturity (referred to as eternal adolescence) (Trimble, 2000).

They may be coded as personality disorders only if present to a degree that interferes significantly with social adjustment.

3.4.4.4.6.1 .Hyper-ethical or hyper-religious groups

3.4.4.4.6.2 Viscous group

3.4.4.4.6.3 Labile group

3...4.10.Mixed (two or more of the above)

3...4.11.Other

Diagnosis should be coded in the category as follows:

- No personality trait accentuation or disorder
- Personality trait accentuation, but not disorder
- Personality disorder specific to epilepsy

Exclude: Patients fulfilling criteria for well-defined DSM-IV or ICD-10 personality disorders.

3.4.4.4.7. Specific Phobic Fears

Specific phobic fears such as fear of seizures (Newsom-Davis, 1998), agoraphobia and social phobia may occur due to recurrent seizures. This may either be part of the interictal dysphoric disorder, in which case that diagnosis is preferred, or alone, in which case they should be coded here. Unlike co-morbid psychiatric disorder, the phobic fears revolve around epilepsy and the fear of the situation and subsequent avoidance is linked to the fear of having a seizure in that situation and the possible consequences.

3.4.4.4.8. Other Relevant Information (to be recorded in all patients if possible)

(1) *Relationship to EEG change*: Characteristic changes in EEG could accompany disorders with psychiatric presentations such as generalised absence status, simple and complex partial seizures, encephalopathy (organic brain syndrome) etc., or there may be an absence or reduction of EEG abnormalities, compared to previous and subsequent EEGs as in forced normalisation. The EEG is thus an important

investigative tool and the findings at the time of psychiatric disturbance need to be coded separately as follows:

- EEG not available/not done
- EEG remains unchanged
- Non-specific EEG change
- Specific EEG change (please specify)

(2) *Anticonvulsant induced psychiatric disorders*: As drugs used in the treatment of epilepsy may contribute to the development of psychiatric disorders, it is important that this is specified as an additional category. As both anticonvulsant induction (Trimble, 1998) and withdrawal (Ketter, 1994) are known to precipitate behavioural change, this needs to be specified, as does the specific anticonvulsant probably responsible, if at all this is possible. This also has prognostic and therapeutic implications, as often the only course of action available to the treating professional is withdrawal of the offending agent.

- Details of AED therapy not known/not documented
- No change in AED treatment
- AED institution (in a 30-day period prior to psychiatric disorder)
- AED withdrawal (in a 7-day period prior to psychiatric disorder)
- Both AED institution and withdrawal during 30-day period
- Note: Specify AEDs

While this classificatory system is by no means the ideal researchers have aspired for, its clinical basis, focus on epilepsy specific psychopathology, and inherent simplicity, are likely to make it applicable in many settings both in the developing/developed

world. This operational system needs to be piloted, suitably modified, and validated in several settings, before it is widely acceptable. Nevertheless, it has provided a template that hitherto did not exist.

3.5. Methodological Issues in Studies of Psychiatric Co-morbidity in Epilepsy

3.5.1. Problems with Ascertainment

Incidence and prevalence figures of epilepsy have varied considerably in different studies with ascertainment methods having a significant role to play (Sander & Shorvon, 2002). Not all patients with epilepsy are aware of their attacks. There is significant under-reporting due to the transient nature of the illness with attacks often going un-witnessed. Medical professionals in primary care have a small number of patients in their register and limited expertise and therefore, patients with epilepsy often do not consult their GP for their seizures, especially if they are in remission (Sander & Shorvon, 1996). There are also problems in making an epilepsy diagnosis even in specialist settings, with 5–20% of all subjects with epilepsy diagnosis being identified to have a non-epileptic attack disorder.

While major psychiatric illness, either schizophrenia like or affective psychosis less often goes un-reported or undiagnosed, common mental disorders may often be missed, and a significant burden of unreported CMD does exist in the community (Jenkins et al., 1998). Co-morbid psychiatric disorder in epilepsy poses other problems as these episodes (both psychotic and affective somatoform) are intimately linked to seizures, are often transient not lasting longer than 72 hours, are

characterised by features such as fatigue and other somatic symptoms (affective somatoform) or confusion and apparent behavioural changes (psychotic) that also are linked with epileptic seizures (Blumer, 2000). Further, these disturbances often do not match conventional descriptions or psychiatric criteria, even when this is clinically applied. Ascertainment of co-morbid psychiatric disorder can therefore be as difficult as the ascertainment of epilepsy.

3.5.2. Problems with Register-Based Studies

Register-based studies rely on the accurate documentation of clinical information. The use of pre-existing records offers a number of advantages. First, such information is relevant to the entire cohort and can be expensive to obtain. In addition, since the data were collected prior to any knowledge of the individual's development of the outcome under study and, in most cases, for reasons totally unrelated to the investigation the use of such information will allow objective and unbiased classification of exposure status, in a cohort design for example. However, the level of detail present in pre-existing records is often insufficient, and data on potential confounding factors is for example often lacking (Hennekens & Buring, 1987). Further, registers rely upon historical information and clinical impressions as documented in the case records, which in turn vary depending on the ability of the individual physician to make accurate diagnosis. Registers may also under-report the burden of psychiatric co-morbidity individuals with less severe illness being left undocumented, while those with more severe problems are included. Further, given the problems in diagnosis and ascertainment at this interface, register-based studies seem inadequate. Nevertheless, a number of studies including some of the most widely quoted studies of psychiatric

epidemiology in epilepsy (Jalava and Sillanpaa, 1996 for example) have relied on case registers.

3.5.3. Problems with Psychiatric Instruments and Criteria

Generic tools used in psychiatric research have been applied in a number of epilepsy studies. The semi-structured clinical examination relies upon the skill and experience of the clinician to reduce measurement error. A degree of structure is introduced to increase reliability. However, the validity of the semi-structured examination has not been the subject of extensive investigation and they have been assumed to bring their credentials with them, from their development with psychiatric patients and their use in clinical research (Dohrenwend, 1995). The use of such instruments in epilepsy settings does confer certain advantages, provided, of course the clinician concerned has expertise in the neuropsychiatry of epilepsy. A variant of this approach is the structured measure, Structured Clinical Interview for DSM (SCID), the Composite International Diagnostic Interview (CIDI), Diagnostic Interview Schedule (DIS), and Clinical Interview Schedule-Revised (CIS-R) all of which rely on trained interviewers in some cases with mental health backgrounds, as opposed to clinical psychiatrists. While these tend to have good psychometric properties, they do not allow unlike their semi-structured peers, the luxury of expert clinical interpretation. Further, these generic instruments do not ask questions relevant to epilepsy, and rely on computer programs and operational rules to generate diagnosis based on standard ICD and DSM criteria, which again do not take into account the psychopathologies specific to epilepsy (Krishnamoorthy 2000a; 2002; submitted).

Other psychometric measures such as the General Health Questionnaire (GHQ), Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory (BDI), Hamilton Anxiety and Depression Ratings Scales (HARS/HDRS), Minnesota Multiphasic Personality Inventory (MMPI), Schedule for Affective Disorders and Schizophrenia (SADS) etc. In general, all these instruments have demonstrated good psychometric properties in relevant populations, both normal individuals and those with psychiatric disorder. Further, the ability of these instruments to identify "cases" with relevant psychiatric disorders is not in question. However, that these are in most cases screening and not diagnostic tools is rather conveniently ignored and several papers are published each year with "psychiatric diagnosis" having been made in epilepsy patients using one of these instruments. The identification of "caseness" without re-confirmation using accepted diagnostic instruments is potentially flawed, and must be approached with caution.

The other potential problem in many studies is the use of criteria such as ICD and DSM. While this results in identification of "cases" as described in psychiatric literature, it is suspected to exclude many cases with disabling clinical psychiatric problems linked to epilepsy, as they fail to meet temporal or other diagnostic criteria. Thus, while a depressive episode needs to last as along as two weeks in ICD-10 (ref.), interictal dysphoric disorder of epilepsy (IDD) is often punctuated by severe but brief bouts of depression, anxiety and other somatic symptoms, which do not last longer than hours to days in many cases (Blumer, 2000). The other problem alluded to elsewhere in this review is the tendency of these systems to label all psychiatric disorders in someone with epilepsy as organic, thus presuming a direct link, which in both clinical and research terms is unhelpful.

3.5.4. The problem of Confounding in Population Studies at this Interface

While a number of potential confounding factors have been identified, aetiology, seizures themselves, and anti-epileptic drugs prescribed for the management of seizures are the three specific confounders that have a significant influence in this interface.

Population-based studies of aetiology in epilepsy are few, limited mainly by costs and logistical problems in carrying out extensive surveys involving neuroimaging and other investigations (Krishnamoorthy, 2003a). As a consequence, studies of aetiology at this interface have largely been hospital-based, and have had conflicting results: some studies linking aetiology to patterns of psychopathology, and others failing to do so. In general, various components of the limbic system and the pre-frontal association cortex have been implicated in schizophreniform and affective illness, co-morbid with epilepsy (Engel et al., 2002). Firm evidence that certain epileptogenic lesions may be associated with certain forms of psychopathology, also emerges from the epilepsy surgery literature, gangliogliomas being strongly associated with psychotic episodes post-operatively (Bruton, 1988) when compared to other developmental lesions associated with epilepsy.

While seizure type and focus have been associated with psychopathology in epilepsy (Bear, 1979), studies attempting to link seizure type and focus with patterns of psychopathology have had conflicting results, both supporting and negating such links. In general, refractory partial seizures arising from the temporal lobe are considered more likely to lead to psychopathology, than other forms of seizures,

depression for e.g., being more likely with complex partial seizures than with generalised seizures (Devinsky & Vasquez, 1993). There are of course specific patterns of psychopathology linked with certain idiopathic generalised epilepsies, Juvenile Myoclonic Epilepsy for example (Trimble, 2000), and these have been associated with frontal lobe dysfunction (Woermann & Duncan, 2000) indicating that anatomical correlates for behavioural dysfunction in epilepsy exist outside the limbic system, as one would expect.

The role of anti-epileptic drugs (AEDs) must also be taken into account, and this is fraught with difficulties. While AEDs have been shown to be thymoleptic and have a significant role to play in stabilising mood and controlling aggression, impulsivity etc. (Post, 1995), they are well known to provoke de novo psychopathology, particularly in temporal correlation with drug introduction, less commonly withdrawal or other change. The commonest anticonvulsant reported to date in the literature as inducing psychoses has been ethosuximide, although it is reasonable to say that nearly all anticonvulsants have at some time been anecdotally reported to provoke these effects. However, some anticonvulsants may be more relevant than others, and efficacy as an anti-epileptic may be correlated with propensity to develop psychopathology (Trimble, 1998). Certainly there has been an upsurge in the reporting of cases in the last decade, with the introduction of new anti-epileptic drugs. These prescriptions essentially have been given as add-on therapy to patients who have not responded to standard anticonvulsant therapy. They are patients who have regular seizures, usually focal, and usually limbic related, which in any case makes these patients susceptible to develop psychopathology (45). Psychosis (5% of cases) and affective disorder (10–15% of cases) have been reported with most new

AEDs including felbamate, lamotrigine, tiagabine, topiramate, vigabatrin and zonisamide (43), often in the context of forced normalisation, not even the newest of AEDs, Levetiracetam being spared (Krishnamoorthy et al., 2002b).

It is not yet clear if any particular chemical class of drugs is interlinked with these problems, although studies to date suggest that drugs that are GABergic may be particularly involved. A further problem to be resolved is the differences between prescribing these drugs in monotherapy as opposed to polytherapy (nearly all the cases reported have been when the drugs have been given as add-on). The extent, to which these problems may occur in patients, for e.g., with less severe forms of epilepsy, who can be managed with monotherapy, is unclear (Krishnamoorthy & Trimble, 1999). Recent literature of interest also includes evidence of AED withdrawal emergent psychopathology (Ketter, 1994), and elegant proposals differentiating AEDs on the basis of cognitive and behavioural symptoms (Ketter, 1999).

3.6. The Assessment of Psychiatric Co-morbidity in Epilepsy

3.6.1. Assessment in Hospital-Based Studies

The vast majority of studies of psychiatric co-morbidity in epilepsy have been hospital-based. Assessment in these studies has varied enormously and included techniques such as retrospective surveys of case notes and unstructured clinical assessments (Currie et al., 1971); screening instruments such as the General Health Questionnaire, Hamilton Anxiety and Depression Rating Scales, Beck Depression

Inventory given alone (Roy, 1979; Mendez et al., 1986); semi-structured interviews such as the Present State Examination (PSE) (Standage & Fenton, 1979); structured tools such as and Structured Clinical Interview for DSM (SCID) (Victoroff, 1994), Clinical Interview Schedule (CIS) (Edeh & Toone, 1987) etc. The latter (semi-structured and structured interviews) have been used to generate ICD and DSM diagnosis. In some cases (Victoroff, 1994, for example) these tools have been adapted for epilepsy, although not always validated. A number of studies have used the Minnesota Multiphasic Personality Inventory (MMPI), and several others the Bear & Fedio Inventory (later Neurobehavioral Inventory (NBI), many with interesting results, and these are reviewed in some detail later in this section.

3.6.2. Assessment in Community-based Studies

Just like hospital-based studies, community-based studies have varied considerably in the techniques of assessment used. A number of these (Bredkjaer et al., 1998 for example) have been register-based and have relied on case registers with their attendant imperfections (reviewed herein). A few have used screening tools to estimate the burden of psychiatric co-morbidity (O'Donoghue et al., 1998 for example) and reported psychiatric caseness on this basis, an approach that may clearly be flawed in the absence of validation. A few others (Edeh & Toone, 1987 for example) have used semi-structured or structured instruments, leading to psychiatric diagnostic criteria-based assessment of caseness. Some studies have employed the Bear & Fedio scale or the Minnesota Multiphasic Personality Inventory (see below) to community-based populations with epilepsy. As far as we are aware, no studies have

compared these methods of assessment in the setting of the community, as we have done in this study.

3.6.3. Measures Commonly Used in Epilepsy Studies

3.6.3.1. The Minnesota Multiphasic Personality Inventory (MMPI)

The Minnesota Multiphasic Personality Inventory is a test used to gather information on personality, attitudes, and mental health of persons aged 16 or older and to aid in clinical diagnosis. It consists of 556 true–false questions, with different formats available for individual and group use. The MMPI is un-timed and can take anywhere from 45 minutes–2 hours to complete. This is normally done in a single session, but can be extended to a second session if necessary. Specific conditions or syndromes that the test can help identify include hypochondriasis, depression, hysteria, paranoia and schizophrenia. Raw scores based on deviations from standard responses are entered on personality profile forms to obtain the individual results. There is also a validity scale to thwart attempts to "fake" the test. Because the MMPI is a complex test whose results can sometimes be ambiguous (and/or skewed by various factors), professionals tend to be cautious in interpreting it, often preferring broad descriptions to specific psychiatric diagnoses, unless these are supported by further testing and observable behavior. A sixth-grade reading level is required in order to take the test. However, a tape-recorded version is available for those with limited literacy, visual impairments, or other problems (Strickland, 2000).

A number of studies in epilepsy and non-epileptic attack disorder, especially those emerging from the North American continent, have used the MMPI. While the validity of this instrument in epilepsy has been questioned (Bear, 1979; Flor-Henry, 1972), there are studies that have indicated its validity in epilepsy (Dikmen et al., 1983). Whitman et al. (1984) used a MMPI sequential diagnostic system to reanalyse 87 published profiles of patients with epilepsy, other neurological disorders and chronic physical illnesses, encompassing a total of 2786 patients. This included 10 studies of epilepsy encompassing a total of 809 subjects. They found that patients with epilepsy were at higher risk of psychopathology than normal controls. However, no difference was found between people with epilepsy and those with other chronic disorders, or between people with TLE and those with generalised epilepsy. A similar investigation was also reported by Dodrill and Batzel (1986) who found that patients with epilepsy demonstrated more psychopathology than normal controls and patients with other neurological disorders, but that there were no differences in rates of psychopathology between TLE and other forms of psychopathology.

3.6.3.2. The Neurobehavioral Inventory for Epilepsy

The Neurobehavioral Inventory (NBI) (Blumer, 1995) was derived from the scale originally developed by Bear and Fedio (1977). They based their questionnaire on behavioural features described in temporal lobe epilepsy, the common manifestations of which best described by Geschwind with contributions to the concept having come from the work of Gastaut (Trimble, 1991). The Bear & Fedio Inventory attempts to determine the effects of a unilateral temporal epileptic focus on specific psychosocial aspects of behaviour. The need to develop such an inventory followed the author's

perception that the MMPI failed to either detect or account for the temporal lobe personality (Bear & Fedio, 1977).

Blumer et al. (1995) have revised the original inventory of Bear and Fedio. The Neurobehavioral Inventory as it is now called thus has a patient and next of kin version (Personal Behaviour Survey) each with 100 questions requiring true and false responses across 20 scales (5 items in each scale). While the questions in the patient version are presented in random fashion and ordered according to scale at the time of scoring, the questions in the carer version are presented in the order of the scales. The interview has a number of personal questions including questions on sexuality, making it difficult for a carer who is not in a cohabiting relationship with the subject, to complete these parts. A total score greater than 20 (true responses) of one hundred, is suggested to be indicative of caseness on this measure. A score of greater than 2 on any scale is taken to indicate a positive rating on that scale. While not validated for general clinical use, the author believes that it facilitates a comprehensive understanding of the psychological changes that may be present specifically in patients with epilepsy.

Studies that have compared patients with temporal lobe epilepsy (TLE) with other groups have tended to show a greater burden of psychopathology as measured by this instrument in the TLE group, although not always with statistically significant differences. Patients with left sided lesions have tended over time to demonstrate a greater burden of psychopathology than those with right sided lesions, although the laterality differences described by Bear & Fedio (1977) have not been replicated in many studies since (Perini, 1986 for example). Studies using the Bear & Fedio scale

have been comprehensively reviewed relatively recently by Trimble (1991) and Shetty & Trimble (1997).

3.6.3.3. The Structured Clinical Interview for DSM (SCID) & the Epilepsy Version (SCID-E)

The Diagnostic Interview Schedule (DIS) lead to controversy about whether a structured interview administered by non-clinicians could yield accurate psychiatric diagnosis. This coincided with the development of the DSM-III and DSM-III-R by the American Psychiatric Association Task Force chaired by Dr. Robert Spitzer, MD. Spitzer concluded that clinicians were necessary for the diagnostic process (Spitzer, 1983), and the need to have a clinician administered diagnostic procedure, which could produce diagnosis according to the latest diagnostic criteria at that time, seemed clear.

Thus began the development of the Structured Clinical Interview for DSM, oriented specifically to DSM-III-R, with the aims that it would be shorter, take less time to administer, require less training and make the diagnostic process shorter than the Schedule for Affective Disorders and Schizophrenia, once training was completed. Hence, nearly all items in SCID are specifically designed to assess DSM-III-R diagnostic criteria, and detailed dimensional information on current status is not obtained (Hasin & Skodol, 1989). The SCID has been adapted to DSM-IV and comes in two major sections: SCID-I is a semi-structured interview for making the major DSM-IV Axis I diagnoses and SCID-II is a semi-structured interview for making DSM-IV Axis II (Personality Disorder) diagnoses. The SCID comes in several

versions: patient, outpatient, non-patient, psychotic symptom screen and exists in both clinical and research versions. A number of software programs that can be used alongside SCID for purposes such as diagnosis generation.

The SCID has been adapted for use in epilepsy patients (Victoroff, 1994) and while this version the SCID-E as it is referred to, has been discussed in epilepsy circles, there is no suggestion that it has been widely used. Comparative data against other common measures of psychopathology is for example not available in populations with epilepsy.

3.7. Methodological Problems in the Assessment of Psychiatric Co-Morbidity at this Interface

A number of methodological issues impact on the assessment of psychopathology in studies of patients with epilepsy and will be reviewed briefly here.

3.7.1. The Generic Nature of Instruments

As reviewed herein, the vast majority of studies have used instruments that are developed for general populations with psychopathology, rather than people with epilepsy. As very specific forms of psychopathology exist in epilepsy, the use of generic instruments alone is inadequate. Thus while the use of generic measures of psychopathology is both important and relevant, especially for the purposes of comparison with population-based controls, the use of measures that are specifically derived to examine psychopathology in epilepsy is extremely important.

3.7.2. The Non-availability of Valid Epilepsy Specific Measures

That having been said, epilepsy specific measures are few and far between. The one measure that was developed specifically for epilepsy, and has seen fairly wide usage in populations with epilepsy, is the Neurobehavioral Inventory (Blumer, 1995). However, its development first as the Bear–Fedio scale and later in its current form as the NBI has been largely opinion led. The instrument arose from the observations of Geschwind, the studies of Bear and Fedio, and most recently the work of Blumer. However, the psychometric properties of this measure have never been examined in any detail, and we have no knowledge of its reliability, validity, sensitivity and specificity. It has also aside from early comparisons with the MMPI (which arguably cannot be described as gold-standard), has never been tested against a gold-standard measure of psychopathology.

3.7.3. A Gold Standard?

But then, is there such a gold standard measure for the assessment of co-morbid psychopathology in epilepsy? At present, no measures exist that have been developed from scratch for the assessment of co-morbid psychopathology in epilepsy populations, using modern techniques of questionnaire development. Instruments widely accepted as close to the gold standard in the assessment of psychopathology in epilepsy, the SCID, SCAN, CIS-R and CIDI have all been used in studies of epilepsy with varying results. Apart from the adapted SCID (SCID-E), none of these other measures has been modified to suit specific issues and concerns in epilepsy. Nor has any one of these been compared against the gold standard of clinician lead diagnosis.

Further, even in the assessment of generic psychopathology in community-based studies, the relative benefits of these various instruments are the subject of considerable debate (Brugha et al., 2001 for e.g.) and there is little consensus about a gold standard. The NBI is therefore by default, the closest we have to a gold standard, albeit a poor gold standard that has not been subjected to the accepted rigors of modern day testing.

3.7.4. Self, Observer/Carer-Rated Measures of Psychiatric Co-Morbidity

A number of studies reviewed herein have used self-rated and interview-based measures that rely upon accurate reporting by the subject about his epilepsy and his emotional state. Epilepsy per se is a highly stigmatising illness, and not surprisingly many patients choose to ignore psychological issues, viewing them as part of the epilepsy process. The measurement of psychopathology at this interface has to be more indirect than within general clinical practice, and the reporting of outcomes is often influenced by the caregiver (Espie et al., 1997). Clinical experience also indicates that even cognitively unimpaired subjects with intractable epilepsy under-report psychopathology (particularly of the ictal variety), and the value of carer reports for the measurement of psychiatric outcome in this population cannot therefore be underscored.

There are however, few carer report-based measures of psychopathology in widespread use, the NBI being an exception. In recent years, a new instrument called the Neuropsychiatric Inventory has emerged. This is a validated informant-based interview, widely used in clinical research studies to evaluate neuropsychiatric

symptoms (Cummings et al., 1994). The NPI has been shown to have adequate test/re-test and inter-rater reliability, and has been used widely to study patients with dementia, as well as a number of conditions in which cognition can be impaired to varying degrees, including Parkinson's disease (Aarsland et al., 1999), multiple sclerosis (Diaz-Olavarrietta et al., 1999), cortico-basal degeneration and progressive supranuclear palsy (Litvan et al., 1998) etc. The instrument is also in use for the differential analysis of behaviours in dementia and as an outcome measure in trials of drugs used in the treatment of dementia (Cummings, 1997).

The use of a carer-rated measure such as this, in combination with self and observer-rated measures is probably appropriate for a complex and chronic clinical disorder such as epilepsy, characterised by episodic alterations in sensorium and progressive memory loss in some cases.

3.8. The Impact of Epilepsy and the Psychiatric Co-morbidity Thereof

3.8.1. Psychosocial Impact of Epilepsy

Epilepsy is a highly stigmatised condition, with social perceptions towards this disorder remaining adverse, even in developed nations (Morrell & Pedley, 2000). It has been shown in a large European study of 5000 people that perceived stigma has a significant impact on quality of life (QOL). Perceived stigma was associated with worry, negative feelings about life, long term health problems, injuries and perceived side effects of medication (Baker, 1998a). The perception of stigma was also strongly associated with QOL in that while 35% of those who described themselves as

delighted with life felt stigmatised, a staggering 79% of those who described life as terrible felt stigmatised.

The impact of epilepsy is revealed in a number of recent comprehensive studies. In a survey of 1023 people with epilepsy in two community-based samples, Fisher et al. (2000) found that patients with epilepsy had less education, were less likely to be employed or married, and came from lower income households. Half the respondents had poor control of their seizures, and most listed uncertainty and fear of having a seizure, as the worst thing about epilepsy. While problems with lifestyle, school, driving and employment limits were all reported, cognitive impairment was ranked highest in a list of potential problems.

In another study, as part of a door–door prevalence study of epilepsy in India (Radhakrishnan et al., 2000), knowledge, attitudes and practices were evaluated in over 1000 subjects from households without epilepsy. Although 99% of the respondents had heard of, or read about epilepsy, there were a number of adverse beliefs. About a third of those surveyed thought that the condition was hereditary. 40% felt that individuals with epilepsy could not be educated or employed properly. 29% felt that a person with epilepsy could not lead a normal married life. 11% even said that they would object to their children being in contact with children who suffered from epilepsy. While women and those with poor education were more likely to hold many of the aforementioned beliefs, men were more likely to regard epilepsy as a mental illness (27% of respondents held these beliefs).

A number of studies have investigated these psychosocial outcomes in different countries, and difficulties in marriage, relationships, employment and emotional adjustment, are reported in most cultures (Mielke et al., 2000; Swinkels et al., 2000).

3.8.2. Seizure Frequency, Severity and Disablement

The efficacy of epilepsy treatment continues to be determined by the rather arbitrary benchmark of a greater than 50% reduction in seizure frequency (Satishchandra and Trimble, 2001). The importance of QOL measures in clinical trials of epilepsy is now well established. However, opinion has tended to vary about the relative importance of seizure frequency and seizure severity, as predictors of QOL, some studies emphasising the importance of seizure frequency (Jacoby et al., 1996) and others the importance of seizure severity (Smith et al., 1991).

Baker et al. (1998b) as part of a cross-sectional, multi-centre, retrospective study of QOL across three European countries – France, Germany and the UK, examined data in 300 patients drawn from 30 neurologists, with information on seizure type, frequency, demographic characteristics and presence of co-morbidities. Seizure frequency was stratified into five groups and classified seizure severity into three increasing classes of severity, simple partial, complex partial, partial seizures evolving into secondary generalisation. The functional status questionnaire (FSQ) a generic measure of QOL (Jette et al., 1986) was used. Those patients who were seizure-free had a significantly better profile on the FSQ than those who were having more than one seizure per-week. The overall trend indicated a worsening of scores on

the FSQ associated with an increase in the frequency of seizures; however several correlations obtained in this regard had potentially weak effects as the author points out. When the 10 relevant FSQ scores across the three participating countries were compared, overall significant differences were obtained for the following domains; mental health, quality of interaction, sexual relations and feelings about health.

Regression analysis of seizure severity lead the authors to conclude that the frequency of more severe seizure types has a more detrimental effect upon patients' QOL than does the frequency of the less severe seizure type. This effect as measured at the 95% confidence level was found for 7 of 10 FSQ scales, and at the 90% level for 9 of 10 scales. Only the mental health scale did not show separation between the impact of seizure frequency across the three seizure types, though it did show a constant decline as severity increased.

3.8.3. The Impact of Psychiatric Co-morbidity on Disablement in Epilepsy

In the study by Baker et al. (1998b) described above, the mental health scales of FSQ were found to be associated both with frequency and severity, and to be affected whatever the type of seizure. Such studies, however, are rare and most have not examined the relationship between psychiatric co-morbidity and disablement while controlling for the effects of seizure related variables. There is considerable evidence however, from primary care studies of depression for e.g., that the level of disablement in these conditions is significant and depression across different levels of severity is a strong predictor of disablement (Kruijshaar et al., 2003). Further, chronic medical illness is strongly associated with psychiatric disorder, with one study

showing ill subjects to have a 41% greater relative risk of co-morbid psychiatric illness when compared with those without medical illness (Rapp et al., 1988). A number of studies have also shown increased prevalence of affective illness in patients with chronic illnesses, diabetes, heart disease, chronic obstructive pulmonary disease (COPD) being examples (Katon & Ciechanowski, 2002). Further, as these authors elucidate depression increases costs; amplifies symptoms of medical illness; increases functional disability; impacts on self-care and adherence to treatment regimens; and increases the risk of mortality (cardiovascular risk in particular). With epilepsy being a chronic illness with significant impact on psychosocial well-being, there seems little doubt the psychiatric co-morbidity will have independent effects on disablement, once seizure related effects have been accounted for. However, we have not come across any published evidence to date in this regard.

3.9. The Treatment of Psychiatric Disorders in Epilepsy

The treatment of psychiatric disorders in epilepsy remains poorly researched and controversial. Thus, the literature on psychiatric management techniques in epilepsy remains largely "opinion lead". Evidence from randomised controlled trials is relatively scant and few systematic investigations have been conducted in this specific area.

There are several controversies that further complicate matters. First, the relationship between epilepsy and psychopathology is by itself controversial. Both agonistic (Slater & Beard, 1963) and antagonistic (Landolt, 1953) relationships have

been proposed, and it is likely that both types of relationships do exist in different individuals and possibly at different times in the same individual.

Second, psychopathology in epilepsy can apparently be provoked by a number of factors, many of which are related to treatment. The seizures themselves (Lancman, 1999), the anticonvulsant drugs used to treat seizures (Trimble, 1998), the withdrawal of anticonvulsant drugs (Ketter, 1994), other biological treatments, epilepsy surgery specifically (Anhoury, 2000) and the social consequences of epilepsy (Fisher et al., 2000) have all been linked to the development of psychopathology.

Third, as it has been pointed out, psychotropic treatments are proconvulsant; both antipsychotics and antidepressants can lower the seizure threshold, and can provoke seizures in those with no past history of seizures (Trimble, 1998). On the other hand, many anticonvulsant drugs have psychotropic properties and some of the best known and most widely used mood stabilisers today are anticonvulsants like carbamazepine, sodium valproate and lamotrigine (Post et al., 1996).

Fourth, the development of psychiatric disorder with the treatment of epilepsy is known to include other biological treatments for epilepsy, thus renewing interest in questions such as the role of seizure cessation in the development of psychopathology. It is interesting too that Electroconvulsive Therapy (ECT), the use of seizures to treat psychiatric disorder, can by increasing the seizure threshold result in a cessation of seizures, at least transiently (Kellner, 1993).

In this section, the management of these disorders is discussed. In the absence of hard evidence from randomised controlled trials, anecdotal experience and the writings of experts have been relied upon.

3.9.1. An Overview of Therapies

The management tools available to the psychiatrist can be broadly classified into – biological and psychological. Of the biological treatments, treatment with psychotropic agents is by far the most popular, antidepressants, anxiolytics, neuroleptics and mood stabilisers being employed extensively. The Serotonin Selective Reuptake Inhibitors (SSRI) have become the antidepressants of choice in epilepsy. Although some interactions, for e.g., fluoxetine and carbamazepine (Spina & Perucca, 2002) or sertraline and lamotrigine (Besag, 2003) have been observed, the SSRIs have a generally low seizurogenic potential and are deemed safe in epilepsy. Indeed, there have been some case reports of a paradoxical improvement in seizure status with the addition of these drugs to the AED regimen. Of the older neuroleptic agents, Haloperidol remains by far the safest drug in epilepsy (McConnell & Duncan, 1998). The newer agents save one exception clozapine (Miller, 2000) generally have less potential to lower the seizure threshold. Sulpiride and risperidone are deemed to be relatively safe and effective drugs to employ (McConnell & Duncan, 1998). Opinion is divided about the seizure potentiating effects of olanzapine, while quetiapine appears to have fewer side effects and a reasonable safety profile (Centorrino et al., 2002). While the use of clozapine is generally discouraged due to its known seizurogenic potential, refractory psychoses of epilepsy does on occasion necessitate its use. A series of patients with intractable psychosis of epilepsy,

successfully treated with Clozapine, has recently been reported (Langosch & Trimble, 2003).

Benzodiazepines, especially those with anticonvulsant properties, lorazepam, clobazam and clonazepam for e.g., can be very effective adjunct agents in anxious, agitated and confused states, leading to the resolution of psychopathology, while helping to maintain or indeed improve seizure control (Allen et al., 2001). The intermittent use of clobazam in loading doses has the potential, both with regard to tacking exacerbations of seizures, and with regard to behavioural exacerbations. Further, as a number of AEDs are thymoleptic, they may help in achieving some control and stabilisation of behaviour. There have been elegant proposals recently that have called for rationalisation of drug therapy-based on the cognitive and behavioural side effects of the AED concerned, activating as opposed to sedating (Ketter et al., 1999). In dealing with a chronic illness, such proposals have value especially as they limit disruption due to intermittent behavioural instability.

Electroconvulsive Therapy, although an important tool in mainstream psychiatry, is rather infrequently employed in subjects with epilepsy, and this too largely in specialist settings. However, new treatments that are shown to have beneficial effects possibly on both seizures and psychopathology have emerged in the past decade, Vagus Nerve Stimulation (VNS) and Transcranial Magnetic Stimulation (TMS) being important examples of such development. The advantage of VNS in epilepsy and co-morbid depression is that it might have positive benefits for both disorders (Harden et al., 2000; Elger et al., 2000). These technologies are however at their infancy, a better understanding of the brain mechanisms they influence is

required, and debates and discoveries are likely to continue for years to come (George, 2001).

A recent meta-analysis of psychological therapies in epilepsy concluded as follows "In view of the methodological deficiencies and limited number of patients studied, we have found no reliable evidence to support the use of these treatments and further trials are needed" (Ramaratnam et al., 2001). The techniques reviewed in this study included relaxation therapy, cognitive behaviour therapy, EEG biofeedback and educational interventions. The caveat of course, was that very few studies were randomised or quasi-randomised, and the vast majority of studies were thus excluded from the analysis.

There is empirical evidence however, suggesting a role for psychological interventions of this nature in subjects with epilepsy. It is common experience in epilepsy units privileged enough to have dedicated psychological support that these methods significantly contribute to effective patient management.

Several models of cognitive behaviour therapy have been applied in epilepsy, ranging from more generic applications of cognitive behaviour theory (Beck, 1993), to rather more specific models based on original research among patients with epilepsy or NEAD (Goldstein, 1990 for review). Cognitive Behaviour Therapy (CBT) as a technique does lend itself to the RCT model of testing. However, with RCTs of even psychotropic treatment in epilepsy being rare, an RCT comparing CBT to other models of psychological treatment may be rather difficult to establish. In general however, as CBT is amenable to adaptation, its use to develop an epilepsy focussed

treatment technique is possible and such efforts merit encouragement. Many treatment teams in specialist centres in the UK, have successfully developed in-house approaches based on the CBT model, and use these to some effect.

The brief form of psychotherapy is another technique frequently used by psychologists. This is usually directed at more psychologically minded individuals, especially those with difficult backgrounds and past emotional trauma, issues that the skilled therapist is able to address. The role of specialist epilepsy nurses must also not be underscored and there is emerging evidence of success with such nurse practitioner interventions (Ridsdale et al., 1999; 2000). Group psychotherapy or patient support groups, family therapy and counselling (often by trained lay counsellors), may all be helpful in the management of patients with epilepsy. There have also been efforts recently to develop neurobehavioral treatments specific to epilepsy (Andrews et al., 2000), and the results of formal trials with such therapies are awaited. Undoubtedly, as the authors of the meta-analysis conclude, randomised controlled trials that meet current scientific standards need to be carried out (Ramaratnam et al., 2001).

All these techniques can be employed singly or in combination in the treatment of psychiatric disorders in the patient with epilepsy. As a general principle as outlined previously in the section on treatment of CMD, it is believed that the combination of biological and psychological treatments is superior to either treatment alone and the vast majority of experts in clinical practice, effectively deploy both avenues individually, in tandem, or sequentially, depending on the complexity of the clinical situation they are faced with.

3.9.2. Management of Epilepsy and Co-morbid Psychopathology in Primary Care

The recent CSAG report (Department of Health, 1999) states that the GP has a central role in the provision of care for patients with epilepsy. However, it also points out that epilepsy is not a condition that should or could be managed in general practice alone. In the primary care setting, dealing with the co-morbidity of epilepsy and psychiatric disorder can be a challenge. This is especially because there is widespread awareness about the seizure potentiating effects of common psychotropic agents (antidepressants for e.g.) and to a lesser extent perhaps of the psychogenic effects of some AEDs. As a consequence, even if psychiatric disorder is identified, it is often un-treated or treated sub-optimally. Further, psychological therapies (apart from counselling) are not generally available in primary care settings and when available are subject to long waiting lists. Mental Health Professionals in these settings also experience difficulties in dealing with the co-morbidity, as their knowledge of epilepsy for e.g., may be limited. The role of the specialist nurse practitioner with both epilepsy and mental health experience is invaluable where available, but sadly they are a rare commodity in UK primary care.

The CSAG report also recommends that practices have a register of patients with epilepsy. It may be wise to red flag cases with co-morbid psychiatric disorder and establish follow-up plans. Group practices or primary care trusts may also seek to identify and develop specialists with higher training in this area. However, with appointments in primary care lasting between seven and half to ten minutes on average in the UK, there is little time for monitoring or performing the duties as suggested above. Further, each GP has relatively few patients with epilepsy, and may

not gain enough experience to feel confident to gain or maintain expertise. Some GPs may be working in isolation and may not be reminded about the importance of regular monitoring and data collection. Further, rapid advances in treatment protocols, and the introduction of new drugs with attendant interactions, often result in the GP finding the new regimen suggested by the consultant difficult to implement, or the complications difficult to manage. Finally, there are in the UK variations in local health authority prescribing guidelines with regard to approved anti-epileptic drug therapy and logistical problems therefore for the GP in continuing a newer AED initiated in hospital but unfamiliar to primary care (Redhead, 2003).

Other problems stem from the stigmatising nature of epilepsy and its effects on employment, marriage, and children. The consequences of the condition such as loss of driving etc., may lead patients to hiding seizure frequency from their doctor (Dalrymple & Appleby, 2000), or indeed co-morbid psychopathology thereof (especially common mental disorders). There is also a risk in this setting that minor psychiatric symptoms like anxiety and depressive symptoms are accepted as part of the epilepsy process, leading thus to a treatment gap. Surveys show that even where a service exists mainly problems of a psychosocial nature continue (Redhead, 2003).

At present, while patients may receive advice and counselling about the consequences and social implications of epilepsy, there is generally no accepted way in which specialists or generalists take responsibility for and allocate time to the provision of this advice (Ridsdale, 1995). There are models of the utilisation of epilepsy liaison nurses working with neurologists in the UK. This has strengthened secondary care. The nurses themselves can then be active in the community visiting

primary care educating patients, practice nurses and GPs. Basic mental health training for all specialist nurse practitioners in epilepsy may be step in the right direction. There are models for nurse-led clinics for patients with epilepsy (Ridsdale et al., 1997). These are well attended, and they have been shown to improve level of advice, reduce hospital admissions, A&E attendances and emergency call outs. Such clinics require disease register, prescription register, re-call system, computer reminders and may stimulate locally agreed protocols. The unique system of patients registering with GPs in the UK allows audit and has been shown to produce important research (Taylor, 1994; Taylor et al., 1994).

The future will reveal whether improved teamwork and communication between primary and secondary care and management plans based on locally agreed initiatives will improve the care of patients with epilepsy, particularly those with a disabling co-morbid psychiatric disorder.

3.10. Studies Conducted as Part of This Thesis

Two studies, one based in an institution for epilepsy, and another based in primary care were conducted as work leading to this thesis. The effort was to study and describe the prevalence and patterns of psychiatric co-morbidity in these different populations with epilepsy; to compare a range of psychiatric measures, generic and specific, as well as self, observer, and carer-rated; and to test specific hypothesis related to the neuropsychiatry of epilepsy. A further analytical component of these studies was to examine the relative contributions of psychiatric co-morbidity and seizure severity to disablement, in both these populations.

The sections that follow will describe the objectives, methods and results in these studies, as well as the in-depth analysis of data using techniques such as factor analysis, Receiver Operating Characteristics (ROC) analysis, generalised linear modelling SPSS, linear regression etc., in an effort to clarify these associations.

SECTION 4:

STUDY I: PREVALENCE, PATTERNS AND ASSESSMENT OF PSYCHIATRIC CO-MORBIDITY IN EPILEPSY- A STUDY IN PRIMARY CARE

4.1 Aims

The primary care study described herein was designed with the following aims:

(1) To estimate the period prevalence of common mental disorder in a representative community-based sample of subjects with epilepsy and to compare this with the period prevalence in matched controls in this population

(2) To compare screening (GHQ-28, HADS & PSQ) structured-diagnostic (Clinical Interview Schedule- Revised (CIS-R) and epilepsy specific (Neurobehavioral Inventory) instruments in a population of subjects with epilepsy, and compare with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) as gold-standard

(3) To examine relationships if any, between psychiatric co-morbidity and seizure severity, and psychiatric co-morbidity, seizure severity and disablement.

4.2. Hypothesis and Estimation of Sample Size

Based on published literature (Edeh and Toone, 1987), we hypothesised that psychiatric co-morbidity will be significantly greater in patients with epilepsy (48%) compared with population-based controls matched for age and sex (20%) (Jenkins et al, 1998). We further hypothesise that specific patterns of psychopathology will help distinguish patients with epilepsy from controls.

The power calculation was based on the aforementioned hypothesis. A sample size of 37 cases and 74 controls would provide 80% power to detect prevalence ratios of 2.4 or greater at 5% significance .

4.3. Setting

The participating centres, King's Lynn in Norfolk and Bradford in Yorkshire, were selected because of the existence in each of a well-maintained community-based register of fully worked up prevalent cases of epilepsy. As will be seen, the registers were differently constituted, but otherwise comparable in cover and detail. The Institute of Neurology has established relationships with those responsible for each of the registers.

4.3.1. Population and Demographic Features

4.3.1.1 King's Lynn, Norfolk

King's Lynn is a small coastal city in the county of Norfolk in Eastern England. An active port, it has two enclosed docks and regular traffic of materials such as timber, steel, chemicals, fertilisers and grain. In mid 1999, the population of King's Lynn and its surrounding parishes was 43,385. The county of Norfolk is mainly rural with a population of 772,000 in seven districts, and a relatively low population density of 144-persons/sq km. Unemployment in the county stands at 4.2% when compared to 3.4% in the eastern region and 4.6% for the UK. The ethnic minority community is less than 1% of the population (national average 5.5%) (www.go-eastern.gov.uk).

4.3.1.2 Bradford, West Yorkshire

Bradford District in 1998 had 486,000 residents, which is expected to grow to 511,000 by 2011. Bradford's reliance on textiles and engineering has given way to high technology and service sector industries, such as finance and exports. A very diverse community, Bradford has, for over a century attracted settlers from Ireland, Germany, many countries in Eastern Europe, and over the last 50 years, countries in the Indian sub-continent and Africa. The city of Bradford has a population of 301,000 people, with diverse conditions of housing and employment, ranging from the older city centre to the new suburbs, which once were free standing villages. 97,000 of Bradford's residents (20%) are Black or Asian, of whom 71,000 (15%) are of Pakistani or Bangladeshi origin. The ethnic minority population is expected to grow to 26% by the year 2011.

4.3.2. Participating GP Surgeries

4.3.2.1. King's Lynn

The population served by St. James House Surgery was 16,878 and that served by Southgate Surgery 7,898. St. James had ten GP Principals in active practice, and Southgate six. St. James serves areas in an around the city centre whereas Southgate serves a more sub-urban and semi-rural population. One of the GP Principals in St. James's House Surgery has a specialist interest in epilepsy, and the practice has an epilepsy nurse specialist who maintains a register; conducts annual review; provides

information, support and counselling services; conducts audits; and maintains links with local support agencies and services.

4.3.2.2. Bradford

Girlington Road Surgery served a population of 7,836 persons in an inner-city area of Bradford, and had 5 GP Principals in active practice. The Ridge Medical Practice (sub-urban) had 10 GP Principals and served 16,358 people, while The Wilsden Surgery had 6 GP Principals and served 9190 people. All three practices came under the Bradford South and West Primary Care Group, subscribed to the Bradford Epilepsy Service, had computerised patient records and were willing to co-operate in this effort, which was the rationale for their choice. There were no GP Principals with special interest in epilepsy in these practices, nor were there any epilepsy specialist nurses directly employed by these practices. However, they had access both to specialist nurses and consultant epileptologist support through the Bradford Epilepsy Service. Patients chosen for this study were drawn from the Bradford Epilepsy Service register.

4.3.2.3. Rationale for Choice of Settings

The two settings for this study were chosen for a combination of pragmatic and scientific reasons. Both settings had links (or were keen to establish links) with the epilepsy programme at the Institute of Neurology and National Hospital. Both settings had recently established primary care-based epilepsy registers, and were willing to allow access to these registers for research reasons. Both settings had potential

collaborators involved closely with the running of epilepsy services and management of the register, who expressed personal interest in this research project being carried out. Both settings had computerised practice registers, and adequate space and facilities for this project.

King's Lynn and Bradford also were thought to be of scientific interest as both settings were somewhat removed from University Centres where neurological services tend to be concentrated, and thus did not have easy access to specialist services. Further, neither population had been recently exposed to large-scale research efforts, a concern with regard to many primary care-based studies in London and other major centres for example.

4.4. Subjects

4.4.1: Establishment of Epilepsy Case Register– St. James' House Surgery, King's Lynn

The case register in St. James' House Surgery in King's Lynn was established during a previous primary care study of epilepsy led from the National Hospital, Queen Square, in which the surgery participated (O' Donoghue et al, 1999). At that time, the disease and drug treatment registers were searched to identify persons having at least one non-febrile epileptic seizure (excluding seizures confined to the first year of life). This had been supplemented by a manual search of medical records, in a proportion of those registered, using the key word "epilepsy". The records of identified cases were then reviewed to determine seizure type, epilepsy syndrome, age at onset, date of

most recent seizure and current treatment status. An epilepsy register was maintained and updated from that time by the GP Principal, with a special interest in epilepsy, and formed the basis for an epilepsy clinic within the practice in which all patients with epilepsy were managed. He is assisted in these duties by specialist nurse practitioner for epilepsy based in the same surgery.

4.4.2. Establishment of Epilepsy Case Register in Southgate Surgery, King's Lynn

As Southgate Surgery did not have an operational epilepsy register, inclusion of subjects from this surgery did not form part of the original study plans in King's Lynn. However, during the investigation in St. James' House Surgery, GP Principals from Southgate Surgery expressed a keen interest in the project and in setting up an epilepsy register in that surgery. As such a measure would also aid local service development significantly, it was decided to adopt similar methods to those used in St. James' House Surgery. As case records in Southgate Surgery were fully computerised, a keyword search (as above), with "epilepsy" and the names of common anti-epileptic drugs as keywords was carried out by the research assistant working on this project. The records of patients identified in this way were scrutinised manually by the research assistant and subjects with diagnosis of epilepsy identified, this being confirmed by this researcher.

4.4.3. Establishment of the Bradford Epilepsy Service and Register

The Bradford Epilepsy Service Register was developed by an epilepsy nurse specialist, searching practice databases using diagnostic codes and from repeat

prescribing data. The nurse reviewed records in 39 practices covering a population of 225,439. We included only those subjects registered with the aforementioned practices. Clinical review was undertaken where there was limited information available in the records. In total, 1643 cases of epilepsy were identified. The data was reviewed by a Consultant Neurologist, and cases with doubtful ascertainment re-examined and classified personally. The register thus developed formed the basis of a unique primary care service, the Bradford Epilepsy Service. This service led by a Consultant Neurologist, assisted by a team including two specialist nurses and a co-coordinator, offers care through community based clinics for epilepsy, held several times every week in community locations around Bradford. The co-coordinator and the specialist nurse practitioners, one with specific interest in learning disability, and another with specific interest in epilepsy, support the service by maintaining a register; conducting periodic reviews; providing information, support and counselling services; and maintaining links with local support agencies and services.

4.4.3.1. Identification of Cases for the Present Study

The aforementioned epilepsy registers formed the basis of case identification. In St. James' House Surgery, King's Lynn, and all three participating surgeries in Bradford, a search of computerised case records was carried out, to further validate the epilepsy register. As in Southgate Surgery, King's Lynn, this used the keywords "epilepsy" and the names of anti-epileptic drugs that were commonly prescribed in the United Kingdom, at the time that this project commenced – phenytoin, carbamazepine, sodium valproate, vigabatrin, lamotrigine, gabapentin, topiramate, and clobazam. This was to ensure that all cases with epilepsy, including those not in the register, or indeed

those that developed epilepsy in the interim period between the establishment of the register and the present study, were identified.

Patients with epilepsy identified in this way were further classified as having active or inactive epilepsy. Active epilepsy was defined using the International League Against Epilepsy"- Commission on Epidemiology & Prognosis (1993) recommended criterion of at least one seizure in the past five years, whether on or off treatment with anti-epileptic drugs. Only cases with active epilepsy were considered for inclusion in the present study. Cases identified in this way were further screened by the research assistant in a telephonic interview, using exclusion criteria for this study.

4.4.4. Exclusion Criteria

- Extremes of age- below 18 and over 70 years
- Cognitive impairment (score of less than 24 on the MMSE)
- Physical disability making participation in study difficult (such as visual or hearing impairment)
- Subjects who do not identify English as being the primary medium of communication

4.4.5. Rationale for Exclusion of Certain Groups

Paediatric epilepsy has been well studied (Menkes, 2000), and consists of spectrum of syndromes of varying aetiology. The diagnosis and clinical features of psychiatric

disorders in children are also somewhat different from those in adults, and hence it was decided that this group should be excluded. We did however include in our study adults who fulfilled criteria for active epilepsy, and in whom epilepsy began in childhood or adolescence.

Older people on the other hand, often have symptomatic seizures that can be attributed to brain injury (cerebrovascular disease for e.g.); degeneration (dementia for e.g.); a spectrum of co-morbidity including psychiatric co-morbidity (subclinical mood disorders for example) (Burke, 2003). Further it was felt that there was too much heterogeneity with older people, both within, and between older and younger people.

There is an over-representation of both epilepsy and behaviour problems in the learning disabled as reviewed earlier herein. It has been estimated that between 15% (mild learning disabilities with IQ>50) and 30% (severe learning disabilities– IQ<50) have co-morbid epilepsy (Corbett, 1988). On the other hand, it has been estimated that around 50% of subjects with mental retardation in a hospital/institutional setting will pose management problems due to psychiatric disturbance (Reid, 1983). Thus, given the background of high psychiatric co-morbidity in the two conditions, i.e., learning disability and epilepsy, one would expect the burden of psychiatric co-morbidity to be significant in cases where both co-exist.

Further, all these populations cannot be assessed in a valid way, using measures of psychiatric co-morbidity (both generic and epilepsy specific) that are widely available to us, and need special measures that are then further validated in

these populations. As this study was intended to be a study of adult, non-learning disabled, non-geriatric subjects with epilepsy, these special groups were not included.

4.4.5.1. Identification of Controls

Controls were identified from the general practice register (computerised) and were the next two persons of the same age and sex on the GP register. Three attempts were made to contact each control subject identified in this way, and if these attempts failed, the next two people matching the description on the GP register were chosen, and approached in a similar way. In this way an effort was made to find two population-based controls for each subject who consented to take part in the study.

4.5. Measures

4.5.1. Review of Case Records

The case records of people identified using the case identification procedure (above) were reviewed. Demographic details were noted, and the records screened to ensure that the subject qualified for inclusion. The diagnosis of epilepsy with a reasonable level of ascertainment and clear documentation was confirmed, and whether subjects thus identified fulfilled criteria for active epilepsy determined. As reliable and consistent data on epilepsy classification is often difficult to obtain in the primary care setting (Commission on Epidemiology, 1993) and brain imaging or EEG were not planned as part of the present study, the decision was made to focus on seizure severity, for the quantification of epilepsy. Seizure severity has been shown to have a

significant impact on disablement (Baker, 1996), and hence this approach was considered to be appropriate.

4.5.2. Mini Mental State Examination (MMSE)

The Mini Mental State Examination (MMSE) (Folstein, 1975) has been used extensively in screening for cognitive impairment. In the USA it was chosen as the sole cognitive component of the Diagnostic Interview Schedule (Robins et al, 1981). The test consists of two parts: verbal and performance. Four verbal sub-tests have a maximum score of 21 points and evaluate orientation in time, memory and attention. Two performance sub-tests have a maximum score of nine points, and involve the naming of objects, execution of written or spoken orders, writing, and copying a complex polygon (Copeland, 1989). In sum the MMSE tests memory, language, praxis and attention and takes between five and ten minutes to administer. It is well validated in hospital populations although the lack of validation work in community and non-hospital populations has been pointed out (Nelson et al, 1986), and is known to be influenced by factors such as ethnicity and socio-economic status (Dick et al, 1984). However, it correlates well with organic changes in the brain (Tsai and Tsuang, 1979), has a well-established cut-off score of 23 or 24 (Anthony et al, 1982), and is one of the most widely used screening tools for cognitive impairment in the clinical setting.

4.5.3. National Hospital Seizure Severity Scale

Seizure severity scales have in recent years been identified as an important additional outcome measure in trials of anti-epileptic drugs. Most available scales share core-components, seizure frequency, seizure type, seizure duration, post-ictal events, post-ictal duration, automatisms, seizure clusters, known patterns, warning, tongue biting, incontinence, injuries and functional impairment (Cramer, 2001). The National Hospital Seizure Severity Scale (NHS3) (O'Donoghue, 1996) was derived from the Chalfont Seizure Severity Scale (Duncan, 1991), and proposed to be refined, quicker and simpler version of the original scale, with better psychometric properties, by the authors. The scale is administered by a health professional during an interview with a patient and a witness to seizures. It derives information about three different seizure types and seven seizure related factors, and generates a score from 1 to 27. An intra-class coefficient of 0.90 was obtained during inter-observer and test-retest reliability assessment, suggesting that the measure is sufficiently reliable for group studies. However, it has been noted that scores for an individual patient should be interpreted with caution in light of the limits of agreement obtained (O'Donoghue, 1996).

4.5.4. Subjective Handicap in Epilepsy (SHE) Scale

The SHE (O'Donoghue, 1998) is a measure of the handicapping effect of epilepsy in daily life. The six sub-scales measure the effect on daily activity ('work/activity'), social life ('Social/Personal'), the physical effects of epilepsy ('Physical), worry and self-confidence ('self-perception'), happiness with life ('Life Satisfaction') and change over the past year ('Change'). All the sub-scales are scored from '0'–'100', '0'

representing the most severe handicap. The scale is specific to epilepsy, has been demonstrated to have good psychometric properties, and has been used in a community-based population with epilepsy with results that compare well with more established generic measures such as the SF 36 (O' Donoghue, 1998). Our choice of an epilepsy specific measure of disablement was because these tend to be condition specific and therefore more responsive. However, they are limited by being not comparable across conditions.

4.5.5. General Health Questionnaire (GHQ)- 28 Item Version

The GHQ is the most widely used screening test and is available in versions as short as 12 items and as long as 60 (Goldberg and Williams, 1988). Since the questionnaire was designed for use in consulting settings, it is focussed on breaks in normal functioning and is concerned with a person's inability to continue with normal healthy functions and experience of new phenomena of a distressing nature. The GHQ assesses "state" not "trait" both because of the "last week" frame it employs, and because of the comparison with "usual".

Each item consists of a question asking whether the respondent has experienced a particular item or behaviour within the previous four weeks on a four-point response scale ranging from less than usual to much more than usual. The GHQ-12 takes only 2 minutes to complete, while the GHQ 60 takes between 10–12 minutes.

The GHQ-28 is a scaled version, which consists of four sub-scales for somatic symptoms; anxiety and insomnia; social dysfunction; and severe depression; which

have been derived by factor analysis. Different scoring methods have been proposed, but the modified scoring method that produces a normal distribution of test scores and hence has better statistical properties is probably preferred. Patients with physical disorders may be over-represented among respondents classified as false positives because of their responses to items concerned with somatic symptoms and social dysfunction (Goldberg and Williams, 1988).

4.5.6. Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression scale was developed by Zigmond and Snaith (1983) in an attempt to overcome a specific problem, that of patients in general hospital practice who have both physical and psychiatric problems. Some of these, for e.g., cardiovascular disease with palpitations, or gastrointestinal disease with constipation or nausea, could give misleadingly high scores on most of the depression and anxiety rating scales, which include somatic symptoms on the basis that they are psychogenic (see GHQ above for example). A scale without this contamination would be valuable in the self-assessment of mood disorders in a general hospital. Depression items were included if they made no reference to physical functions. Anxiety items were included from the Present State Examination, although as the items in the PSE are mainly autonomic in nature, surprise has been expressed about this choice of source instrument (Thompson, 1989). In a medical population the depression scale correlated 0.70 with an independent global rating, and the anxiety scale 0.74. Each sub-scale was independent in that they failed to correlate significantly with the rating of the other mood (Zigmond and Snaith, 1983). The scale scores were independent of

physical illness, as physically ill patients with low global severity scores of either depression or anxiety scored very low on the questionnaire (Thompson, 1989).

4.5.7. Clinical Interview Schedule (Revised)

The Revised Clinical Interview Schedule (CIS-R) (Lewis et al, 1992) is a standardised semi-structured interview to assess the mental state of subjects with non-psychotic psychiatric disorders. The revised version, unlike the original, does not require the interviewer's clinical judgement so minimises observer bias. Most aspects of the interviewing style are prescribed by the interview, including the exact wording of the questions and specific rules for coding each symptom. The revised version is suitable for use by lay interviewers. The CIS-R limits the period of interview to the previous week, on the ground that memory for psychological symptoms, and thus validity of responses, becomes poor when a longer period is used. However, the subject is also asked about the total duration of symptoms.

The instrument has 14 sub-sections: somatic symptoms, fatigue, concentration, sleep problems, irritability, worry over physical health, depression, depressive ideas, worry, anxiety, phobia, panic, obsessions and compulsions. Scores for sub-sections range from 0–4 (0–5 for depressive ideas). The ratings obtained at interview provide a score for each section, which together can be summed up to yield an overall score, which is taken to indicate the severity of any minor psychiatric disorder. A cut-off score of 11/12 has been validated to determine caseness (Lewis et al, 1992). Algorithms using CIS-R data can be employed to generate ICD-10 diagnosis of mild, moderate and severe depressive episodes, agoraphobia, social phobia, panic disorder,

generalised anxiety disorder, obsessive compulsive disorder and neurasthenia. The CIS-R has been shown to have high inter-rater reliability (Lewis et al, 1992) and has been employed in many investigations of non-psychotic psychiatric morbidity.

4.5.8. Psychosis Screening Questionnaire (PSQ)

The Psychosis Screening Questionnaire (PSQ) was specially developed for the National Psychiatric Morbidity Surveys of Great Britain (Jenkins et al, 1997), as no suitable pre-existing screening questionnaire was available. The PSQ comprises of 12 questions than enquire about positive psychotic symptoms in the preceding 12 months and in preliminary testing in a clinical population it performed well (Bebbington & Nayani, 1995). Two main problems have been identified. First, even with high sensitivity and specificity, the positive predictive value of a test becomes quite poor when the prevalence of a condition is low. Second, the instrument failed to identify those with a past history of psychotic symptoms who were in remission, as they did were not experiencing any current psychotic symptoms. In the psychiatric morbidity survey these limitations were overcome in part by screening for anti-psychotic medication and contact with a mental health professional (Jenkins, 1997). However, given the higher proportion of cases with psychosis even in population samples with epilepsy (Krishnamoorthy, 2001), and the relative absence of validated measures to screen for psychotic symptoms in the community, the PSQ was chosen as a screening tool in this study.

4.5.9. Neurobehavioral Inventory (NBI)

Reviewed in detail in the epilepsy and co-morbid psychopathology section (3.6.3.2, pg 130).

4.5.10. Schedules for Clinical Assessment in Neuropsychiatry (SCAN) & Present State Examination (PSE)

The SCAN system (WHO, 1992) was developed jointly by the World Health Organisation and (WHO) and the National Institutes of Health (NIH). SCAN represents the latest stage in a 30-year strategy of development that began in the 1950s (with the PSE versions 7, 8 and 9). SCAN consists of a set of instruments to assess, measure and classify psychopathology and the behaviour associated with the major psychiatric syndromes of adult life.

It has four components: the tenth edition of Present State Examination (PSE 10), the Glossary of Differential Diagnosis, the Item Group Checklist (IGC) and Clinical History Schedule (CHS).

The PSE 10 itself has two parts. Part one covers somatoform, dissociative, anxiety, depressive and bipolar disorders, problems associated with basic bodily functions, the use of alcohol and other substance use. Part two covers psychotic and cognitive disorders with observed abnormalities of speech, affect and behaviour. Data from the schedules can be recorded in a variety of ways; on the SCAN schedules themselves, on coding booklets, on the free entry record booklet, into the computer data entry

program, by employing a computer program to administer SCAN, the new version being a WINDOWS version (WHO, 1995). A set of computer algorithms (CATEGO) is used to process data entered from SCAN schedules. The output is presented as a series of options including a range of profile of symptoms and IGC scores, an index of definition, ICD and Diagnostic and Statistical Manual categories, and a pre-diagnostic profile of categories. In its complete form SCAN is meant only for use by clinicians with knowledge of psychopathology who have taken a course at a WHO designated training centre. Although, exhaustive in its coverage, SCAN is time consuming.

In this study the main component of the SCAN that was employed was PSE 10. The interviews were performed by this researcher who was blinded to responses to the other instruments employed in this study, at the time of carrying out the PSE interview. Sections 2–12 of the PSE interview (Part I-Neurosis) were completed in all subjects, as was Section 14 the screening section for Part II (Psychosis). Part II was completed for all subjects who failed the psychosis screening.

4.6. Protocols and Procedures

4.6.1. Preliminary public education programme (King's Lynn)

Although there was an established epilepsy service in St. James's House Surgery, there had been no programme of on-going education or public communication on epilepsy. The GP Principal and his team felt that the proposed study would therefore provide an opportunity to educate those in their register and other interested members of the public about epilepsy. The target audience for this programme was patients,

their carers, patient interest groups and lay members of the public. The announcements and invitations were done through personal contact, flyers, posters and announcements in the local radio station. The objective was to increase awareness and to encourage the establishment of a local interest group.

The programme was conducted by staff from the Centre for Education, National Society for Epilepsy- Centre for Epilepsy, Chalfont St. Peter, Buckinghamshire, UK. No specific mention of the proposed research project was made, although interested members of public were told that some research in collaboration with the National Hospital in London was expected to commence soon. The programme was well attended, with around 80 people taking part, and engendered considerable interest.

4.6.2. On-going Public Communication (Bradford)

The Bradford Epilepsy Service, as an independent primary care service, has an on-going programme of public communication, including a periodic newsletter, flyers, posters, announcements in local media etc. As this was an on-going process, it was opined that an educational programme similar to that in King's Lynn was not a specific need, and information about this on-going study would be disseminated among those in the service register.

4.6.2.1. Rationale

The obvious concern in supporting an educational programme in one study setting and not in the other was how this might differentially affect response rate in the present study. In both settings, there was no specific effort to advertise the study, given ethical concerns in this regard. Apart from the measures outline herein, any mention of the proposed study in both settings, via these public communications was therefore incidental. After consultation we concluded that the effect of the on-going communication in Bradford was likely to match the educational programme that was held in King's Lynn, and these effects on the response rate (if any) would be negligible.

4.6.3. Role of Epilepsy Nurse Specialists in King's Lynn and Bradford

As the study was taking place off site (outside London and away from the sphere of the National Hospital's influence) and in primary care, it was opined by local collaborators in both settings, that supportive contact of individual subjects by these specialist nurses was essential and desirable. Further, epilepsy nurse specialists in both settings had close contact with subjects on the study register, and were in the majority of cases familiar with individual subjects. They were therefore charged with the responsibility of informing subjects that the proposed study was imminent, and to expect contact from the research assistant. While these efforts were primarily taken to reassure potential participants that their local service was involved in the current research effort, they may have augmented response rates, and this is to be acknowledged.

4.6.4. Invitation to Subjects

A letter was sent to all potential subjects inviting them to take part in this study. In King's Lynn, the letters were in the respective letterheads of the two practices that were taking part, and were co-signed by the GP Principal co-coordinating the effort in that surgery and this investigator (section 9.8; pg. 435).

As the Bradford Epilepsy Service had direct contact with the potential subjects in all three participating surgeries, the letters in that setting were on the letterhead of that service and were co-signed by the lead consultant heading the service and this investigator. Information sheets outlining the nature and purpose of the proposed study, accompanied the letters in both settings (section 9.8; pg. 435).

4.6.5. Protocol with Non-Responders

Non-responders were sent a second letter of invitation after a two-week period. If there was no response to this second letter within a month, a third letter was sent out. If no response was received after all three letters the subject was considered a non-responder, and no further attempts at contact made.

4.6.6. Protocol with Responders

Responders were contacted by the research assistant responsible for the project, and an appointment arranged for the first phase assessment. This they were told could take

place either at their own GP surgery, or at home, whichever they preferred most. They were also reminded that assessment by this investigator maybe necessary within 30 days of this first phase assessment.

4.6.7. First Phase Assessment by Research Assistant

The research assistant met with participants by appointment. These meetings took place either in the GP's Surgery where the patient was registered, in a consulting room allocated for that purpose, or if the patient were to so prefer, in the patient's own home. The assessment began with an explanation about the study, formal completion of informed consent procedures and brief review and clarification of records. At this stage subjects also handed in self report measures sent to them, GHQ-28 and HADS for cases and controls, and in addition the SHE and NBI measures for subjects with epilepsy. All participants were assessed using the mini-mental state examination, and those who obtained a score of less than 24 excluded from the study at this stage. In reality, due to careful screening procedures, very few subjects were excluded at this stage. Subjects completed the CIS-R (computer self-report version) in the presence of the RA, were screened with the PSQ by the RA, and those in the epilepsy group were in addition interviewed with the National Hospital Seizure Severity Scale.

4.6.8. Second Phase Assessment by this Investigator

All subjects with epilepsy seen in phase 1 and all controls identified to have co-morbid psychiatric disorder in Phase I were invited to attend a second appointment with this investigator, during which clinical diagnosis of epilepsy was clarified, and

subjects interviewed using the SCAN. This interview was conducted either in the GP surgery or in the subject's residence, depending on his/her preference. To ensure that there was concordance between the screening data and SCAN data, all SCAN interviews were accomplished within the period during which prevalence of psychiatric disorders was being studied (30 days). The two stage approach to assessment was preferred as it lent clarity to the process both for patient and investigator; shortened the overall assessment time, which would otherwise exceed three hours in subjects taking part in the SCAN interview, as well as other measures; and was widely endorsed by the GP's taking part in the study. This investigator remained blinded to the results of all screening instruments at the time of conducting the phase II interview, in an effort to minimise bias.

This investigator reviewed all subjects in the control group who were positive on either the CIS-R or PSQ, and those with clinically significant psychopathology brought to the attention of their General Practitioner, in line with good clinical research practice.

Patients with epilepsy responded to the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) administered by this investigator, using the computer assisted interview program, WINDOWS version 2.1.

The responses were rated in two ways. First, the algorithms in the WINDOWS programme were run, in the conventional manner, to elicit ICD-10 diagnoses. Given the relatively small size of the sample, ICD-10 diagnoses were coded in the following broad categories: organic mental disorder; substance abuse disorder; psychoses;

mania or cyclothymia; depression, dysthymia, other unspecified mood disorder; anxiety or phobic disorder; somatoform disorder; eating, sleep, sexual disorder.

Second, this investigator rated each symptom category for clinical significance, this being defined as the presence of three or more symptoms in each broad symptom category. These categories followed the PSE sections and were: somatoform; worry; anxiety; phobia; obsession; depression; dysthymia; thinking; sleep, appetite & sexual symptoms; alcohol; substance abuse; psychotic symptoms. An overall rating of clinical significance was also made; subjects were rated to have clinically significant psychiatric symptoms if they had positive ratings in two or more PSE symptom categories. This rating of clinical significance was undertaken, as it has been frequently observed that patients with epilepsy have clinically significant psychopathology that fails to achieve diagnostic significance using conventional criteria.

4.7. Ethical Issues

4.7.1. Ethics Committee Approval

Local Area Ethics Committee approval was sought and obtained both in King's Lynn and in Bradford. In King' Lynn, the GP Principal in St. James' House Surgery Dr. Keith Redhead was a co-applicant, and in Bradford the Consultant Neurologist heading the Bradford Epilepsy Service, Dr. Nigel Hakin, was a co-applicant.

4.7.2. Consent

Procedures for informed consent were followed carefully. Subjects were sent an invitation to participate and an information sheet (Appendix- section 9.8). The information in these was verbally reiterated by the RA who also provided clarifications if any were required. This investigator contacted those subjects requiring further clarifications. All subjects completed and signed consent forms in the presence of the RA, and these were witnessed by another person- either an accompanying relative/friend/carer of the subject, or a member of the surgery staff.

4.7.3. Confidentiality

Data was entered directly into the statistical program for social sciences (SPSS) windows version 10.0. Data was code and password protected with only this investigator and RA able to access data files.

4.7.4. Rewards and Inducements

Taxi fares were reimbursed for all patients who attended research appointments in the GP surgery in exchange for receipts. Patients seen at home did not receive any financial reimbursement. While participation lead to a discussion of clinical issues and on occasion a review of clinical care with the concerned GP principal or consultant as appropriate, no special inducements in terms of patient care were offered in advance of patient assessment.

4.7.5. Clinical Issues

A decision was made at the outset of the study that if subjects were identified to have clinically significant psychiatric symptoms this would be brought to the attention of their GP, for appropriate action. Informed consent was obtained on this basis. In both locations community mental health teams were informed about the proposed study and the possibility that an increased throughput of referrals may be expected during the course of this study. Arrangements were also set in place to deal with psychiatric emergencies if any were to emerge during the study process.

4.8. Statistical Methods

Data was entered on to the statistical program for social sciences (SPSS) WINDOWS version 10.0. All analysis was carried out using SPSS for WINDOWS version 10.0

Psychiatric measures used were considered in the following categories for the purpose of meaningful comparison. The GHQ-28 and HADS were considered as generic screening measures used widely in psychiatric research, the former in population studies and the latter mainly in hospital-based studies. The CIS-R was considered a generic diagnostic instrument that generates ICD-10 diagnosis of common mental disorder. The NBI was considered an epilepsy specific measure of psychopathology.

Two gold standards measures of psychiatric caseness were used in this study. The Collins English Dictionary (1984) defines a gold standard as "a monetary system in which the unit of currency is defined with reference to gold". In clinical science and epidemiology, gold standard is used to imply a measure of such standard that other measures could be compared with or alternately aspire to match.

At the first level of comparison, the screening instruments HADS & GHQ-28 were compared with the structured clinical interview the CIS-R, which can be used to generate ICD-10 criteria based psychiatric diagnosis. In the next level of comparison, HADS, GHQ-28 & CIS-R were compared against the ICD-10 diagnosis based ratings of psychiatric caseness derived from the PSE interview. These instruments were also then compared with a clinical significance gold standard.

4.8.1. The Clinical Significance Gold Standard

As conventional psychiatric diagnostic criteria have been deemed insensitive to identifying Neuropsychiatric disorders in epilepsy, we decided to assume a clinical significance gold standard in addition to the ICD-10 diagnosis based gold standard. The clinical significance gold standard was a decision on psychiatric caseness made based on multiplicity of symptoms. If the participant reported 3 or more symptoms in one symptom category in the PSE/SCAN (for e.g., anxiety) then they were considered to be a case. This kind of decision-making based on operational rules has precedence in psychiatric research, and in particular was used in the WHO primary care study of psychological disorders (Ustun & Sartorius, 1995).

We therefore compared in stages:

(1) Cases and controls across GHQ-28, HADS and CIS-R using independent samples *t*-test for continuous measures and the chi-square test with Yates correction and Fisher's exact test for categorical data. Symptom categories across measures were compared using Spearman correlations. A paired samples t-test was employed to compare cases and controls.

(2) Cases were further assessed by comparing GHQ-28, HADS and CIS-R data with the two gold-standard measures of psychiatric caseness- ICD-10 diagnosis generated from the SCAN interview, and the clinical significance gold-standard. ROC analysis (described below) was used to study these associations and to establish sensitivity, specificity, and optimal cut-off scores to determine psychiatric caseness in epilepsy in each of the instruments.

(3) NBI patient and carer scales were also subjected to a range of comparisons. First both patient and carer scores were compared with CIS-R and the two gold standard measures for psychiatric caseness to determine cut-off scores in this population. Second, NBI patient and carer scales were compared for agreement in symptomatology.

In depth analysis comparing the performance of different instruments against "gold-standard" measures was assessed using Receiver Operating Characteristics (ROC) analysis. Details of this procedure are reviewed here.

4.8.2. Receiver Operating Characteristics (ROC) Analysis

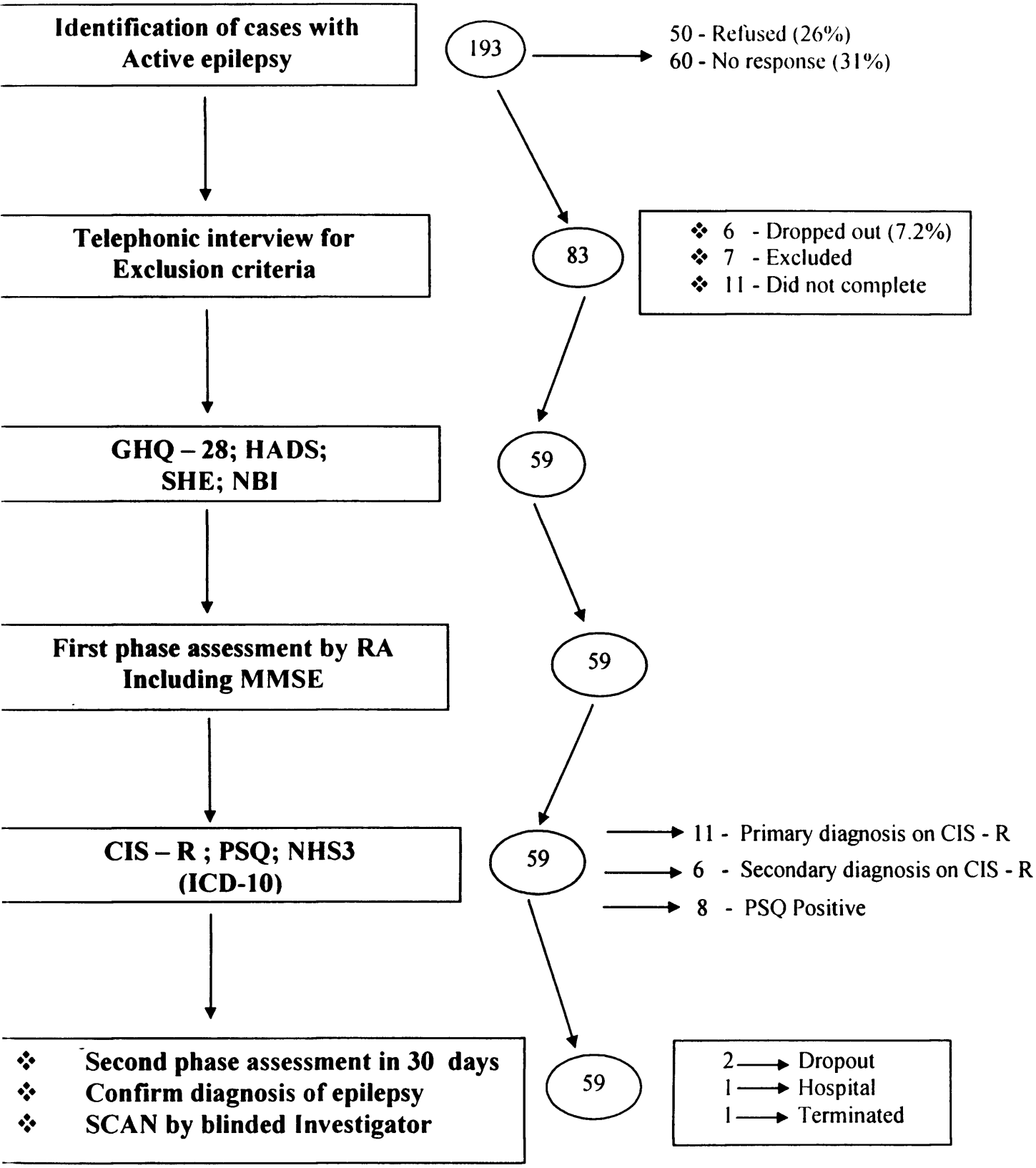
This technique was originally developed for use with radar to separate observed variability from innate detectability of a signal (Swets, 1964). It produces a curve, which has been described as "a function, which summarises all possible noise". It is thought to be particularly useful in epidemiological research, and several investigators have used this form of analysis in psychiatry (Goldberg & Williams, 1998).

This technique can be used to assess the ability of a screening instrument to discriminate between "cases" and "non-cases" using different threshold scores (i.e., the discriminating ability of an instrument across the total spectrum of morbidity, rather than limiting the scope of a validation study by presenting the sensitivity and specificity at a single chosen threshold score), and it has the advantage of enabling clinicians to compare the relative performance, in terms of discriminating power, of two or more competing screening instruments.

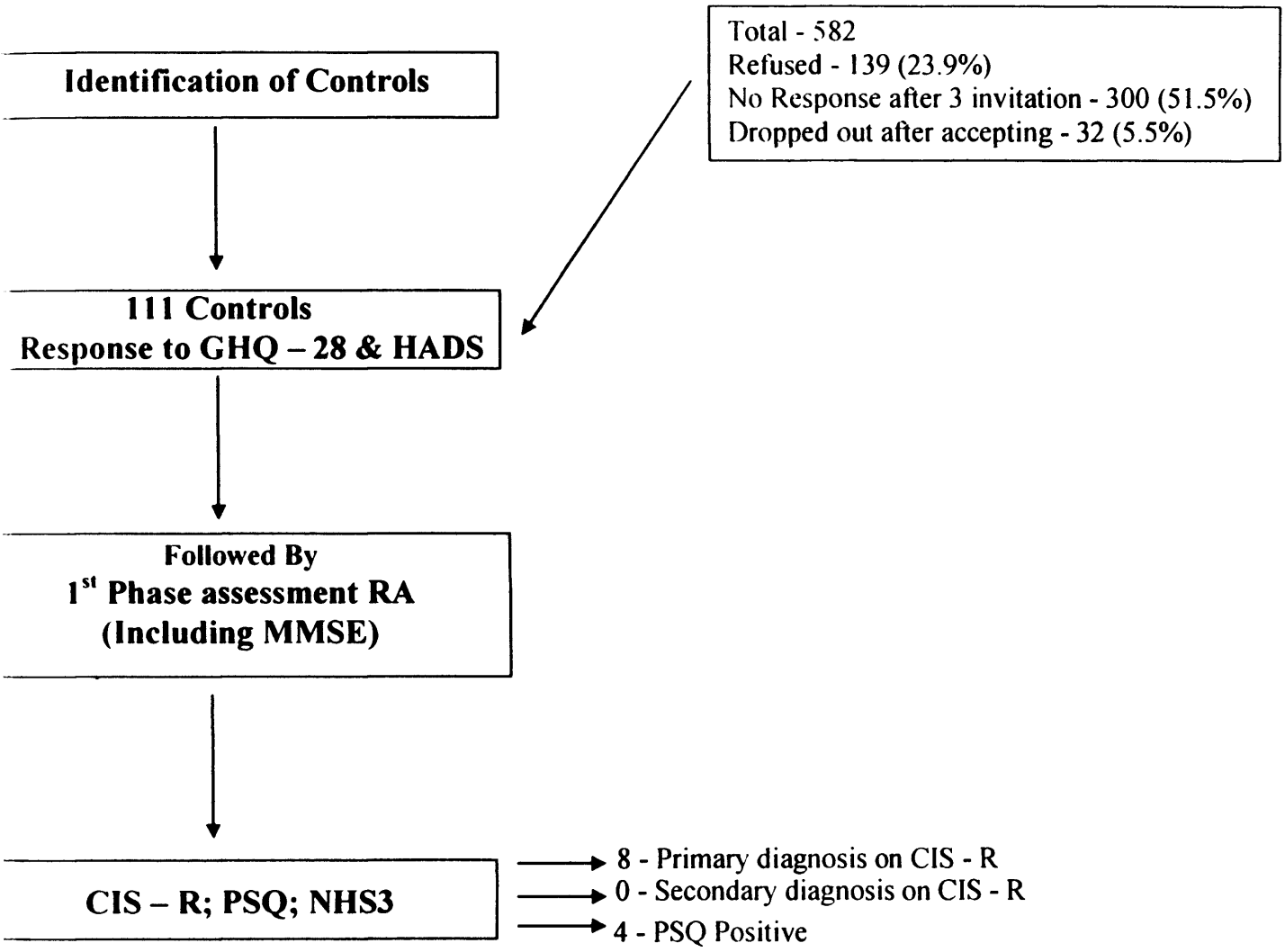
To apply this technique, true positive rate (sensitivity) and false positive rate (1-specificity) are calculated from the contingency tables drawn up for each possible threshold score. By plotting these against each other for each threshold score, a graph is constructed and the area under the ROC curve summarises the discriminating performance. The area can vary from 0.5 (a test with no useful discrimination) to 1.0 a test with perfect discrimination.

A Synopsis of the study methods in flow chart form is presented in the following pages.

Study I : Primary Care - Cases



Study I : Primary Care - Controls



5. RESULTS FROM THE PRIMARY CARE STUDY

5.1. Demography & Response Rates

5.1.1. Subjects

A total of 193 subjects with epilepsy were identified to meet inclusion criteria for the study and invited to take part. Of these 83 subjects (43%) accepted the invitation to participate. Fifty subjects (26%) refused, and no response was received despite three letters of invitation in 60 cases (31%).

Of those who accepted, 6 subjects (7.2%) dropped out after initial acceptance, and 7 (8.4%) met exclusion criteria when interviewed in phase I and were thus found to be unsuitable. A further 11 (13.3%) did not complete the study. 59 of the 83 who initially agreed to take part (71.1%) completed the study and form the case group.

5.1.2. Controls

A total of 582 controls were identified and invited to take part in the five practices. The selection and invitation of controls took place in two stages in each surgery as described in the methods section (4.4.4.1, pg. 160). 143 (24.5%) of those invited agreed to participate, and 139 (23.9%) refused. 300 of 582 subjects (51.5%) failed to respond after three letters of invitation. Of the 143 who initially agreed to participate, 32 (22.4%) dropped out. 111 of 143 control subjects who originally accepted (77.6%) our invitation, took part in the study and form the control group.

111 population based controls (at least one per case) were recruited to take part in this study. While the case-control study was originally designed for matched pairs, we could not for all cases manage to recruit two, or for some cases even one suitably matched control (next person of the same age and sex in the GP register). Therefore, in general we carried out unmatched analyses. We did, however, have 51 closely matched pairs and for this subset of participants we tested the main hypothesis using appropriate statistical tests, taking account of the matching.

Table-2 details response rates by setting.

Table 2. GP surgeries & response rates.

Surgery	No. Invited	No. accepted	No. of dropouts	No. unsuitable	No. who did not complete	No. of refusals	No response
KING'S LYNN St. James' House							
Patients	60	36	1	5	2	14	10
Controls	200	50	3	0	0	45	105
Southgate							
Patients	30	15	3	0	4	6	9
Controls	60	20	6	0	0	10	30

BRADFORD							
Wilsden							
Patients	30	10	2	0	1	10	10
Controls	60	15	5	0	0	17	28
Ridge							
Patients	48	12	0	0	2	14	22
Controls	164	38	12	0	0	40	86
Girlington							
Patients	25	10	0	2	2	6	9
Controls	98	20	6	0	0	27	51

Fifty-nine subjects from general practice case-registers for epilepsy and 111 controls from the same practices were identified as meeting inclusion criteria for the study. Thirty of these subjects with epilepsy (50.8%) came from the two practices in King's Lynn, and the remaining 29 from the three practices in Bradford. 61 of the control subjects (55.0%) came from the two practices in King's Lynn, and the remaining 50 controls from the three practices in Bradford.

5.1.3. Comparisons between Study Locations

When the two locations were compared:

- The acceptance rate (patients who responded to invitation and agreed to take part):
  - For patients 51/90 (56.6%) in King's Lynn and 32/ 103 (31.1%) in Bradford (Chi Square (Yates corrected) = 11.82; p= 0.006)
  - For controls 70/ 260 (26.9%) in King's Lynn and 73/ 322 (22.6%) in Bradford (Chi Square (Yates corrected) = 1.18; p= 0.28)
- The refusal rate (patients who were contacted and refused to take part):
  - For patients 20/90 (22.2%) in King's Lynn and 30/ 103 (29.1%) in Bradford (Chi Square (Yates corrected) = 0.86; p= 0.36)
  - For controls 55/260 (21.2%) in King's Lynn and 84/322 (26.1%) in Bradford (Chi Square (Yates corrected) = 1.66; p= 0.19)
- The non-responder rate (patients who did not respond to 3 invitations):
  - For patients 19/90 (21.1%) in King's Lynn and 41/103 (39.8%) in Bradford (Chi Square (Yates corrected) = 6.99; p= 0.008)
  - For controls 135/260 (51.9%) in King's Lynn and 165/322 (51.2%) in Bradford (Chi Square (Yates corrected) = 0.01; p= 0.93)
- The drop out rate (after having agreed to take part):
  - For patients 4/51 (7.8%) in King's Lynn and 2/32 (6.3%) in Bradford (Chi Square (Yates corrected) = 0.03; p= 0.87)
  - For controls 9/70 (12.9%) in King's Lynn and 23/ 73 (31.5%) in Bradford (Chi Square (Yates corrected) = 6.12; p= 0.01)
- The non-completion rate (attended but could not complete interview):

- For patients 6/47 (12.8%) in King's Lynn, and 5/30 (16.7%) in Bradford (Chi Square (Yates corrected) = 0.02; p= 0.89)
- No controls failed to complete the study in either location.

Patients with epilepsy were significantly more likely to agree to take part (p=0.006), and to respond to the invitation (p=0.008) in King's Lynn than in Bradford. Control subjects in Bradford were significantly more likely to drop out, having agreed to take part (p=0.01). There were no other differences between the two populations in terms of response.

We could not examine further associations between failure to respond, age, gender, social class, co-morbid illness etc. not having collected this data at the time the study was carried out. This was partly due to local reasons with practitioners in both King's Lynn and Bradford being keen that we did not a. contact individuals directly unless they responded to the initial invitation and b. not include data on individuals who had not given informed consent to be thus included.

5.1.4. Age

At the time of the study, the youngest participant with epilepsy was 21 years old, and the oldest 70 years old. The youngest person in the control group was 20 years old, and the oldest 69 years old. The mean patient age was 46.6 years and the mean control age 49.8 years. The median patient age was 46.0 years and the median age for controls 50.0 years. When patient and control groups were compared for age overall,

no statistical differences were found between patient (mean 46.6 years) and control (mean 49.8 years) groups (p=0.483).

5.1.5. Sex

There were 29 females and 30 males in the patient group; and 51 females and 60 males in the control group. There were no statistically significant differences between the two groups (Chi Square- Yates Corrected= 0.06; p= 0.81; OR= 0.88).

5.2. Common Mental Disorders in Patients with Epilepsy and Controls

5.2.1. CIS-R in Patients and Controls

Derived from the CIS-R (and based therefore on ICD-10 criteria), 11 of 59 cases with epilepsy (18.6%) had a primary psychiatric diagnosis (CMD). In comparison 8 of 111 subjects (7.2%) in the control group were identified to have a primary psychiatric diagnosis (CMD) the difference being statistically significant (Chi Square Yates Corrected= 3.99; p=0.045; OR= 2.95 (1.02-8.68)). The primary psychiatric diagnosis in the patient and control groups, are detailed in Table 3.

Table 3. Primary psychiatric diagnosis.

		Subject group		Total
		Controls	Patients	
Primary psychiatric diagnosis	Mild depressive episode	2	1	3
	Mixed disorder	6	4	10
	Moderate Depressive episode		1	1
	Specific (isolated) phobia		1	1
	Obsessive –compulsive disorder		2	2
	Severe depressive episode (F32.2)		1	1
	Social phobia		1	1
	No diagnosis identified	103	48	151
Total		111	59	170

Six of 59 patients with epilepsy and none of the controls had a secondary psychiatric diagnosis, the difference being statistically significant (Chi Square Yates Corrected-8.90; Fisher's Exact Test p= 0.001 (two tailed)). The secondary psychiatric diagnoses were agoraphobia (1), mild depressive episode (1), mixed disorder (1), obsessive-compulsive disorder (1), panic disorder (1), social phobia (1); figures in brackets indicating patient numbers affected.

We compared mean total scores on the CIS-R between patient and control groups, using the independent samples t-test. There was a significant difference between the two groups, patients with epilepsy having a mean score of 8.85 when

compared with the control mean of 4.51 (t= −2.729; p= 0.008; Mean difference -4.33; CI: 1.17 to −7.49).

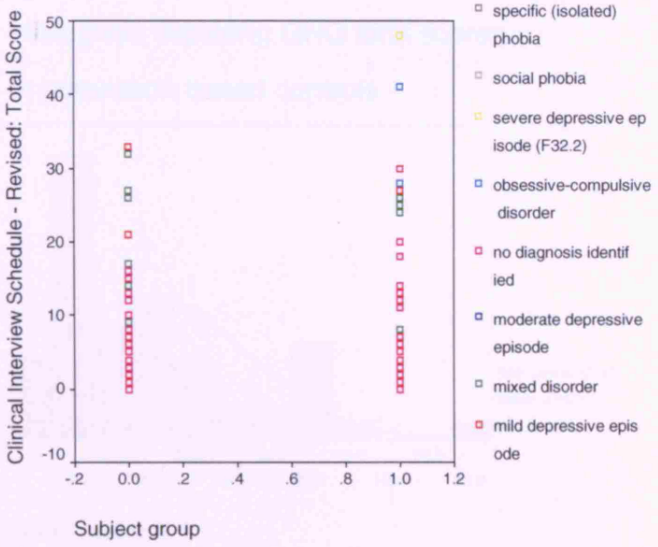
As described earlier, while the case-control study was designed for matched pairs, we did not in fact manage to recruit two matched controls (next person of the same age and sex in the GP register) for each subject. We did have however 51 matched pairs (persons with epilepsy and matched controls) and examined if the difference was significant in the two groups using the McNemar Chi Squared test. Patients with epilepsy were notably more likely to suffer from a common mental disorder, however this trend did not quite reach statistical significance (OR=4.0 CI 0.9–18.8; p= 0.06; Chi Sq 1 DF= 3.6).

Differences in the pattern of common mental disorder symptoms between the epilepsy and control groups were compared using the independent samples t-test. Patients with epilepsy were more likely to suffer from poor concentration (p=0.003); depression (p= 0.006); worry (p= .009); worry over physical health (p=0.05); compulsions (p=0.036). Irritability, depressive ideas and anxiety approached but failed to achieve significance. There were no other statistically significant differences in terms of CIS-R symptoms the results being expressed in Table 4 and Figure 1.

Table 4. CIS-R symptoms in patients and controls.

CIS-R Symptoms	*t*	Df	Sig. (2-tailed)	Mean Difference	Std. Error	95% CI	
						Lower	Upper
Somatic symptoms	−0.54	168.0	0.591	−0.08	0.15	−0.37	0.21
Worry over physical health	−1.99	82.1	0.050	−0.29	0.15	−0.58	0.00
Fatigue	−1.00	168.0	0.321	−0.23	0.23	−0.70	0.23
Sleep problems	−0.86	168.0	0.392	−0.16	0.19	−0.53	0.21
Irritability	−1.88	94.9	0.063	−0.37	0.19	−0.75	−0.02
Poor concentration	−3.06	90.2	0.003	−0.50	0.16	−0.82	−0.18
Depression	−2.80	71.7	0.006	−0.43	0.15	−0.73	−0.12
Depressive ideas	−1.84	83.9	0.069	−0.39	0.21	−0.81	−0.03
Phobias	−1.51	168.0	0.132	−0.12	0.07	−0.27	0.03
Worry	−2.66	84.5	0.009	−0.49	0.18	−0.85	−0.12
Anxiety	−1.88	87.7	0.063	−0.35	0.19	−0.73	0.02
Panic	−1.56	168.0	0.120	−0.14	0.08	−0.31	0.04
Compulsions	−2.13	68.2	0.036	−0.24	0.11	−0.47	−0.02
Obsessions	−1.462	168.0	0.146	−0.22	0.15	−0.52	0.08

Figure 1. CIS-R symptoms stratified by primary psychiatric diagnosis.



5.2.2. Common Mental Disorders: Comparisons between Screening and Diagnostic Measures in Patients and Controls

Figs 2–9 (histograms) depict the distribution of scores in the two screening measures, GHQ-28 & HADS, and the structured diagnostic measure the CIS-R, in both patient and control groups.

Figure 2. Histogram depicting GHQ total scores in population-based controls

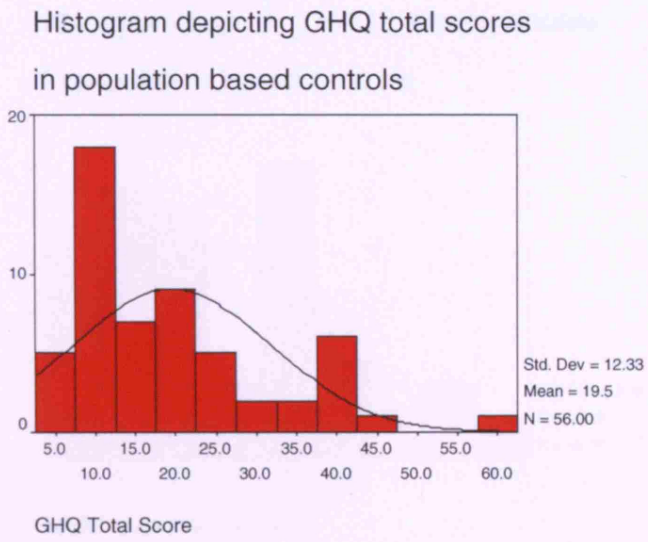


Figure 3. Histogram depicting the GHQ total scores in patients with epilepsy.

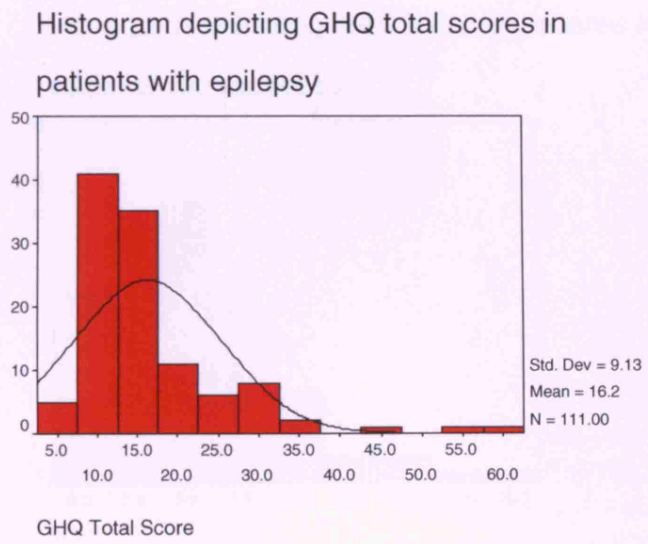


Figure 4. Histogram depicting HADS Anxiety scores in population-based controls.

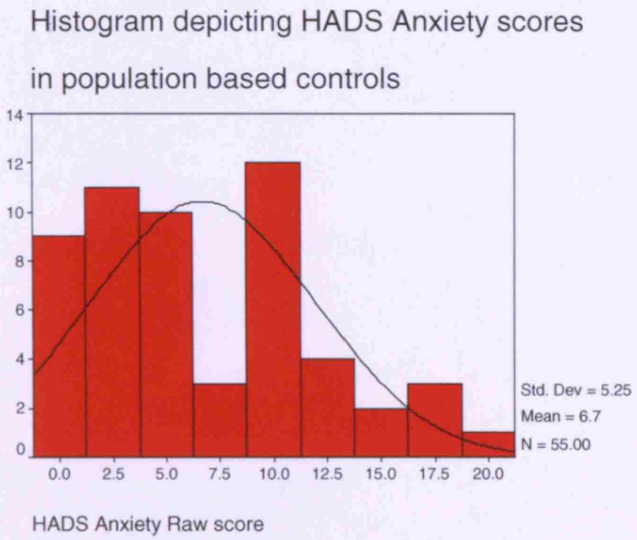


Figure 5. Histogram depicting HADS Anxiety scores in patients with epilepsy.

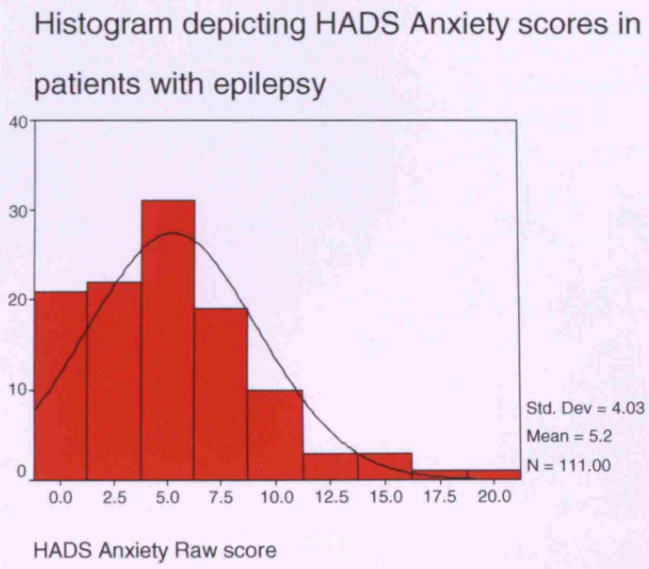


Figure 6. Histogram depicting HADS Depression scores in patients with epilepsy.

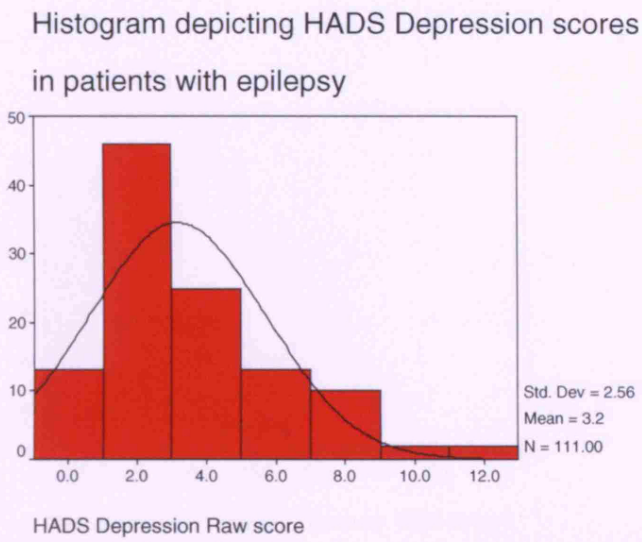


Figure 7. Histogram depicting HADS Depression scores in population-based controls.

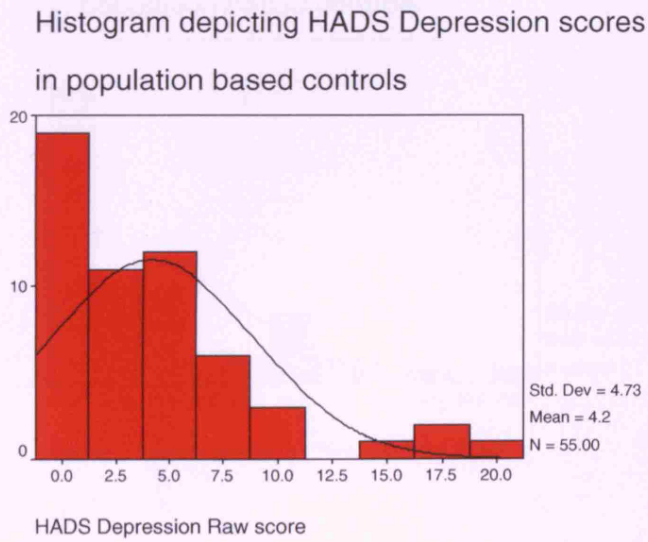


Figure 8. Histogram depicting CIS-R total scores in patients with epilepsy.

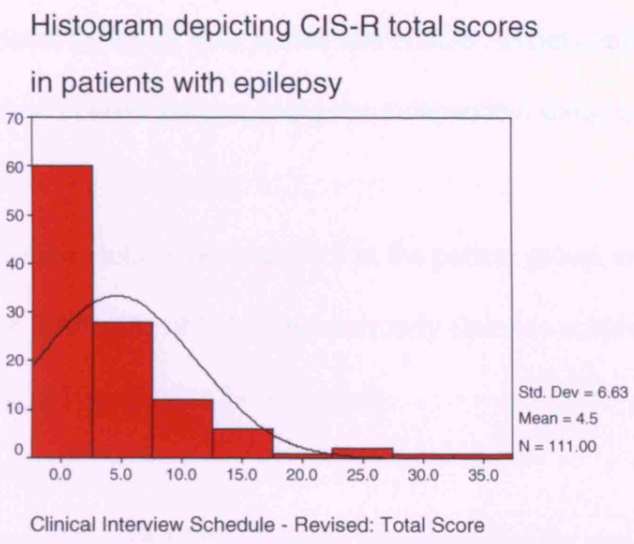
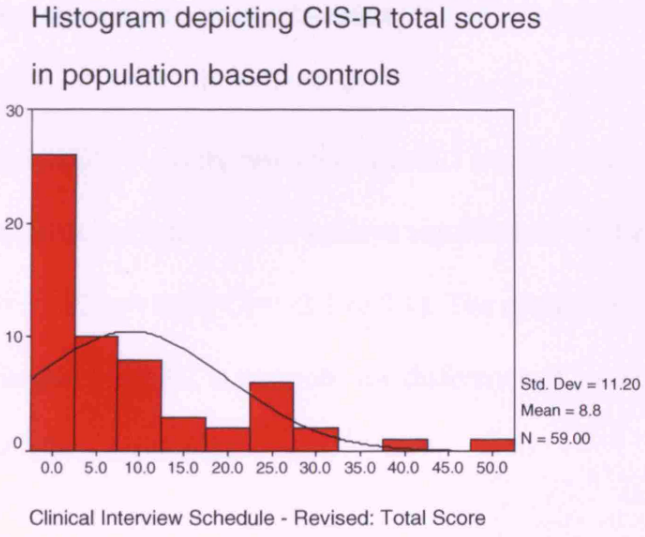


Figure 9. Histogram depicting CIS-R total scores in population-based controls.



In line with prediction, both case and control group scores are positively skewed, indicating that a greater proportion of subjects irrespective of group have below average scores on these measures, with a minority recording markedly high levels of morbidity.

We compared GHQ-28 total scores and HADS Anxiety and Depression raw scores in patient and control groups, using the independent samples *t*-test.

The mean GHQ total score was 19.5 in the patient group, and 16.2 in the control group; the difference of 3.3 points narrowly failed to achieve statistical significance (t= 1.793; p= 0.08; CI= −7.0–0.4).

When the scaled GHQ-28 responses were compared in patients and controls across the four constituent scales: somatic symptoms, anxiety and insomnia, social dysfunction, and depression; only somatic symptoms were found to be significantly more common in the cases (mean= 5.6) than controls (mean= 3.9) (t= 2.7; p= 0.007; CI: -2.9 to -.5). There was a non-significant trend for difference between cases and controls in the anxiety and insomnia sub-scales (t= -1.9; p= 0.06; CI: −2.9 to 6.9).

The mean HADS- Anxiety raw score was 6.7 in cases and 5.2 in controls; this difference also approached but failed to achieve significance on the independent samples *t*-test (t= −1.83; p= 0.07; CI= −3.1 to 0.1). The mean HADS- Depression raw scores were 4.2 in cases and 3.2 in controls, the difference of 1.0 not being significant (t= −1.5; p= 0.14; CI= −2.4 to 0.3).

We compared cases as detected by the HADS Anxiety and Depression sub-scales in patient and control groups using the Chi Square test. 13 of 55 (23.6%) of cases and 11 of 111 (9.9%) of controls were identified as cases on the HADS Anxiety sub-scale using the published cut-off score of 8 and above as being positive, the difference being statistically significant (corrected Chi Square= 4.6; Fisher's Exact test p= 0.03 two tailed). Six of 55 (10.9%) cases, and 2 of 111 (1.8%) controls were identified as cases on the HADS Depression sub-scale, the difference being statistically significant (corrected Chi Square= 4.8; Fisher's exact test p= 0.02 two tailed).

5.2.2.1. Comparison between Generic Screening Measures (GHQ-28 & HADS) and the Diagnostic Measure (CIS-R) in Cases and Controls

We examined non-parametric correlations between the screening instruments for CMD, GHQ-28 (total score) and HADS (anxiety and depression raw scores), and the gold-standard structured diagnostic instrument, CIS-R (total score) separately in both patients with epilepsy and controls. While the spearman correlations were generally significant at the p= 0.01 level (Tables 5 & 6), there was generally greater agreement between the instruments in controls as compared to cases.

Table 5. Non-parametric correlations between screening and diagnostic instruments in population-based controls.

			GHQ	HADS Anxiety	HADS Depression	CIS-R
Spearman's RHO	GHQ total score	Correlation Coefficient	1.00	0.75	0.75	0.81
		Sig. (2-tailed)		<0.001	<0.001	<0.001
	HADS Anxiety raw score	Correlation Coefficient		1.00	0.77	0.78
		Sig. (2-tailed)			<0.001	<0.001
	HADS Depression raw score	Correlation Coefficient			1.00	0.76
		Sig. (2-tailed)				<0.001
	CIS-R: Total score	Correlation Coefficient				1.000
		Sig. (2-tailed)				

Table 6. Non-parametric correlations between screening and diagnostic instruments in patients with epilepsy

			GHQ	HADS Anxiety	HADS Depression	CIS-R
Spearman's RHO	GHQ Total Score	Correlation Coefficient	1.000	0.49	0.51	0.53
		Sig. (2-tailed)		<0.001	<0.001	<0.001
	HADS Anxiety Raw score	Correlation Coefficient		1.000	0.60	0.50
		Sig. (2-tailed)			<0.001	<0.001
	HADS Depression Raw score	Correlation Coefficient			1.000	0.45
		Sig. (2-tailed)				<0.001
	CIS-R: Total Score	Correlation Coefficient				1.000
		Sig. (2-tailed)				

5.2.3 ROC Analysis comparisons of screening measures with the diagnostic measure (CIS-R) in patients with epilepsy and controls

We tested the ability of the screening instruments, GHQ-28 and HADS, to discriminate psychiatric cases from non-cases, when compared to the gold-standard structured clinical instrument, the CIS-R, in both epilepsy and control groups. CIS-R caseness was decided based on the recommended cut off value of 12 (Lewis G, 1992). The total GHQ-28 score, the HADS Anxiety raw score and the HADS Depression raw

score were compared using Receiver Operating Characteristics Analysis (Section 4.8.2; pg. 178).

Of 55 patients with epilepsy in whom complete data on all instruments was available, 40 were non-cases on CIS-R and 15 were cases. GHQ-28 and HADS Anxiety and Depression scales were comparable as measures of psychiatric caseness, when compared to the CIS-R gold standard. Fig-10 and Table-7 depict and detail the area under the curve for GHQ-28 and HADS Anxiety and Depression sub-scales.

Figure 10. ROC Curve comparing GHQ-28 & HADS with CIS-R as gold standard in patients with epilepsy.

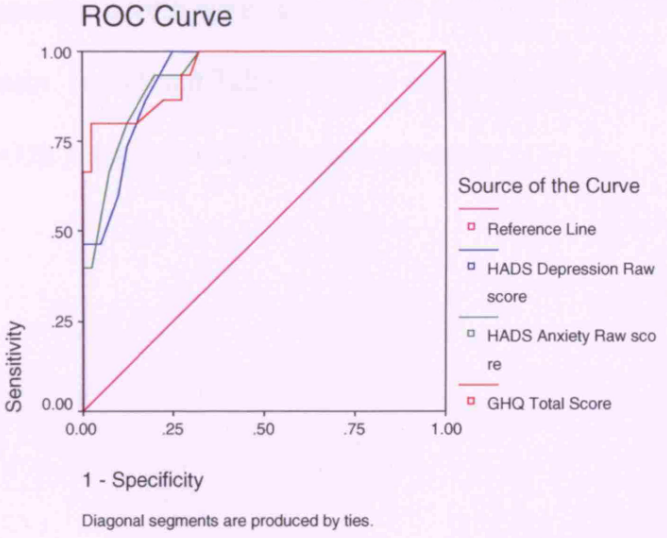


Table 7. Area under the ROC curve comparing GHQ-28 and HADS with the CIS-R Gold Standard in patients with epilepsy.

	Area	Std. Error	Asymptotic 95% CI	
Test result variable(s)			Lower bound	Upper bound
GHQ total score	0.95	0.03	0.88	1.00
HADS Anxiety raw score	0.93	0.03	0.87	1.00
HADS Depression raw score	0.93	0.03	0.86	0.99

Of 111 controls, 99 were non-cases on CIS-R and 12 were cases. GHQ-28 and HADS Anxiety and Depression scores were compared as described above, as measures of psychiatric caseness. Fig-11 and Table-8 depict and detail the area under the curve for GHQ-28 and HADS Anxiety and Depression sub-scales.

Figure 11. ROC Curve comparing GHQ-28 & HADS with CIS-R as gold standard in population based controls.

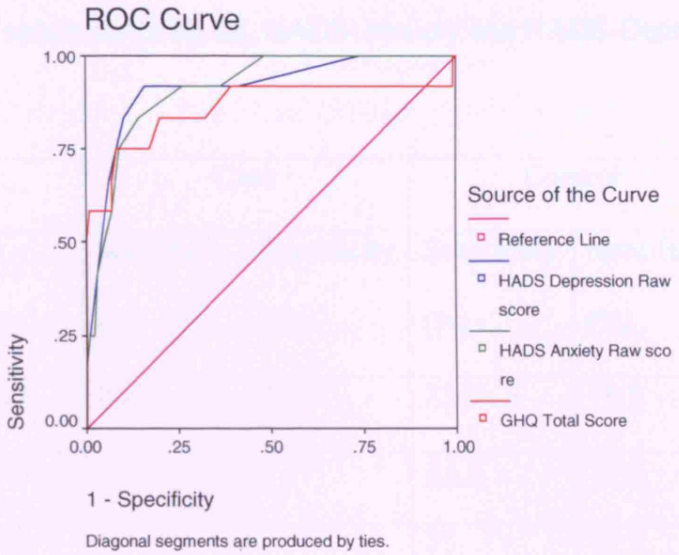


Table 8. Area under the ROC curve area under the ROC curve comparing GHQ-28 and HADS with the CIS-R gold standard in controls.

	Area	Std. Error	Asymptotic 95% CI	
Test result variable(s)			Lower bound	Upper bound
GHQ total score	0.86	0.08	0.70	1.00
HADS Anxiety raw score	0.91	0.04	0.84	0.99
HADS Depression raw score	0.91	0.05	0.82	1.00

The cut-off scores in Table 9 achieved the best match of sensitivity and specificity, with lower scores in the control group generally being discriminative of psychiatric caseness, when compared with the patient group. The scores that simultaneously optimised sensitivity and specificity were chosen as the optimal cut point.

Table 9. Cut-off values for GHQ-28, HADS-Anxiety and HADS-Depression.

		Case		Control	
Scale	Cut point	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
GHQ-28	16/17	86.7	77.5	83.3	76.8
	17/18			83.3	79.8
	18/19			75	82.8
	19/20				
	20/21				
	21/22	80.0	85.0		
	22/23	80.0	87.5		
	23/24	80.0	92.5		
	24/25	80.0	95.0		
	26/27	80.0	97.5		
	27/28	73.3	97.5		
HADS-A	6/7	93.3	72.5	91.7	73.7
	7/8	93.3	77.5	83.3	85.9
	8/9	93.3	80.0	75.0	90.9
	9/10	80.0	87.5		

HADS-D	3/4	100.0	75.0	91.7	73.7
	4/5	86.7	82.5	91.7	83.8
	5/6	73.3	87.5	83.3	89.9
	6/7			66.7	93.9

5.2.4. Psychotic Symptoms in Patients in Controls

Eight of 59 patients and 4 of 111 controls were rated positive on the psychotic symptom questionnaire, the difference being statistically significant on the Chi Square test (Chi Square: Yates Corrected- 4.4; Fisher's exact test p= 0.025, two tailed; OR= 4.20; 95% CI 1.2–14.6).

5.3. Psychiatric Disorders in Patients with Epilepsy

As the cases (patients with epilepsy) had also been administered the SCAN and NBI measures, we proceeded to examine the response to these measures and compared the same with the generic screening and diagnostic measures described in the previous sections.

5.3.1. Psychiatric symptoms as rated using the PSE components of the SCAN

Fifty-five of 59 patients completed the SCAN interview. Of the remaining four subjects, two failed to attend the second stage interview despite being contacted on three separate occasions, and two others could not complete the interview, one due to serious physical illness resulting in hospitalisation and subsequent failure to recover

adequately, and the other requested termination because the content was distressing to her.

Depressive and anxiety disorders were the most common ICD-10 psychiatric disorders overall in this population, with psychoses, mania/cyclothymia, alcohol and substance abuse, and somatoform disorders being relatively uncommon. ICD diagnosis (broad categories) identified in this patient sample are shown in Table 10.

Table 10. ICD-10 Diagnostic Categories in patients with epilepsy.

ICD diagnostic category	Number rated positive (n=55)	(%)
Alcohol & substance abuse	2	3.6
Psychoses	1	1.8
Mania/cyclothymia	1	1.8
Depression	12	21.8
Anxiety/ other neurosis	10	18.2
Somatisation	2	3.6
Eating, sleep, sexual dysfunction	5	9.1
Any ICD diagnosis	16	29.1

As described previously, we also rated clinically significant PSE symptoms in this population. Impaired biological functioning (weight, appetite, sleep, sexual functions); anxiety and phobic disorders; depression (including dysthymic symptoms)

were common, while symptoms of psychoses, obsessions and compulsions, alcohol and substance abuse were uncommon in this population. PSE symptoms rated by the investigator to be "clinically significant" are shown in Table 11.

Table 11. Clinically significant psychiatric symptoms in patients with epilepsy.

PSE Symptom	Number clinically significant N=55	(%)
Somatoform symptoms	10	18.2
Worry	16	29.1
Anxiety & panic	16	29.1
Phobia	15	27.3
Obsessions	3	5.5
Depression	10	18.2
Persistent depressive symptoms	8	14.5
Impaired thinking, concentration, interests	13	23.6
Impaired weight, appetite, sleep, sexual function	19	34.5
Eating disorder symptoms	4	7.3
Symptoms of hypomania, mania, cyclothymia	2	3.6
Alcohol abuse	2	3.6
Substance abuse	1	1.8
Psychosis	3	5.5

5.3.2. "Clinical Significance" and ICD-10 Diagnosis as Measures of Psychiatric Caseness

We examined agreement between psychiatric caseness derived via ICD-10 diagnosis (i.e., ICD-10 criteria were met) and psychiatric caseness derived by the clinical significance ratings (psychiatric caseness decided on the basis of 3 or more symptoms in one category being present-described earlier herein). The kappa for the agreement between caseness based on PSE symptoms and caseness based on ICD diagnosis was 0.762.

5.3.3. Agreement between CIS-R and SCAN Ratings

We examined agreement between psychiatric caseness ascertained via CIS-R using ICD-10 diagnostic criteria and psychiatric caseness ascertained via SCAN using ICD-10 diagnostic criteria. The kappa for the agreement between psychiatric caseness based on CIS-R derived ICD-10 diagnosis and PSE/SCAN derived ICD-10 diagnosis was 0.604.

5.3.4. Agreement between CIS-R and "Clinical Significance" Ratings

We also examined agreement between psychiatric caseness derived from CIS-R using ICD-10 criteria and psychiatric caseness as defined by clinical significance ratings. The kappa for agreement between CIS-R derived ICD-10 criteria and PSE/SCAN derived ratings of clinical significance was 0.417.

5.3.5. Performance of the GHQ-28, HADS & CIS-R against the ICD-10 and "Clinical Significance' Gold-Standards

We used receiver operating characteristics (ROC) analysis to study the relative ability of the screening instruments GHQ-28 and HADS, and the structured diagnostic instrument CIS-R to discriminate psychiatric cases and non-cases when compared to the gold-standards: SCAN derived ICD-10 criteria based diagnosis and clinical significance ratings of psychiatric caseness. Figures 12 & 13 depict the ROC curves, and Tables 12 & 13 the area under the curve for ICD-10 diagnosis and caseness based on PSE clinical significance respectively.

Figure 12. ROC curve comparing screening and diagnostic measures with ICD-10 diagnosis derived by SCAN interview in patients with epilepsy.

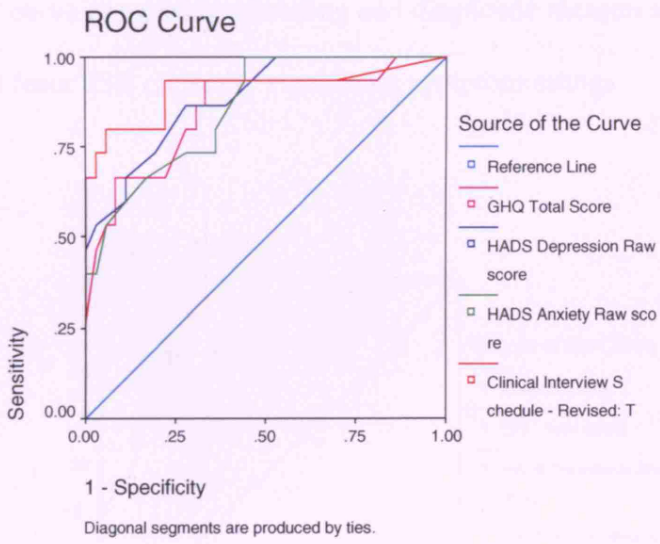


Table 12. Area under the ROC curve comparing the performance of screening and diagnostic measures against the ICD-10 diagnosis gold standard.

	Area Std. Error		Asymptotic 95% Confidence Interval	
Test result variable(s)			Lower Bound	Upper Bound
Clinical Interview Schedule - Revised: Total Score	0.90	0.06	0.80	1.00
HADS Anxiety Raw score	0.85	0.05	0.75	0.96
HADS Depression Raw score	0.88	0.05	0.79	0.98
GHQ Total Score	0.85	0.06	0.73	0.98

Figure 13. ROC curve comparing screening and diagnostic measures with psychiatric caseness derived from PSE clinically significant symptom ratings.

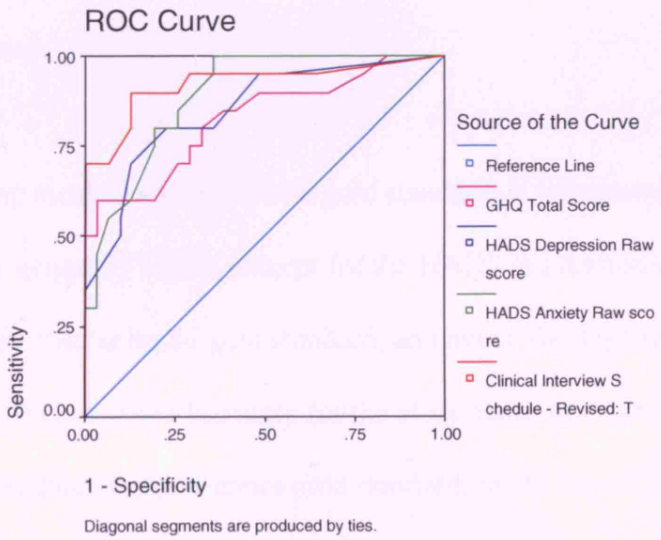


Table 13. Area under the ROC curve comparing the performance of screening and diagnostic measures against the clinical significance gold standard in patients with epilepsy.

	Area	Std. Error	Asymptotic 95% confidence interval	
Test result variable(s)			Lower bound	Upper bound
Clinical interview schedule - revised: Total score	0.92	0.05	0.84	1.00
HADS Anxiety raw score	0.89	0.04	0.81	0.98
HADS Depression raw score	0.85	0.06	0.74	0.96
GHQ total score	0.83	0.06	0.71	0.95

In both cases the CIS-R performed best in relation to the gold standard, followed by HADS scales and GHQ-28, in that order. The area under the curve is greater with the clinical significance gold standard, as compared with the ICD-10 diagnostic criteria based gold standard.

Comparing measures with the two gold standards it becomes apparent that the cut-off scores are generally higher (except for the HADS depression scale) with the ICD-10 diagnostic criteria based gold standard, and match those generally recommended in the published literature for the aforementioned instruments. However, with the clinical significance gold standard, lower cut-off scores generally

result in the best match of sensitivity and specificity. The implications of these findings will be addressed in the discussion section. The range of scores, sensitivity and specificity figures are given in Table 14 with the recommended cut-off values derived from optimal matching of sensitivity and specificity, with each instrument, being underlined.

Table 14. Sensitivity, specificity and cut-off values, of GHQ-28, HADS, and CIS-R, against the 2 gold standards, Clinical Significance diagnosis, and ICD-10 diagnosis.

Scale	Score (CS diagnosis)	Sensitivity (%)	Specificity (%)	Score (ICD diagnosis)	Sensitivity (%)	Specificity (%)
GHQ	18/19	75.0	71.0	17/18	86.7	69.4
	19/20	70.0	71.0	19/20	80.0	69.4
	20/21	70.0	74.2	20/21	80.0	77.2
	21/22	60.0	80.6	21/22	66.7	77.8
HADSA	5/6	85.0	74.2	5/6	80.0	63.9
	6/7	80.0	74.2	6/7	73.3	63.9
	7/8	80.0	80.6	7/8	73.3	69.4
	8/9	75.0	80.6	8/9	73.3	72.2
	9/10			9/10	66.7	83.3
HADSD	2/3	80.0	64.5	2/3	86.7	61.1
	3/4	80.0	77.4	¾	86.7	77.2
	4/5	70.0	87.1	4/5	73.3	80.6
CIS-R	5/6	90.0	80.6			

	6/7	90.0	87.0	6/7	93.3	77.8
	7/8	80.0	87.0	7/8	80.0	77.8
	8/9			9/10	80.0	88.9
	9/10			11/12	80.0	94.4
	10/11			12/13	73.3	94.4

5.3.6. Performance of the Psychotic Symptom Questionnaire against the ICD-10 and "Clinical Significance" Gold Standards

Although CMD were the focus of our study, we applied the psychotic symptom questionnaire as a screening instrument for psychosis. Even a single positive response among five responses, is considered to be positive for psychosis on this measure. Eight of 59 subjects were rated as PSQ positive.

We compared the psychotic symptom questionnaire as a screening measure of psychiatric caseness with the two gold standards: SCAN derived ICD-10 criteria based diagnosis of psychosis and "clinical significance" ratings. Three of 55 subjects interviewed were rated as having clinically significant psychotic symptoms, in comparison to one of 59 subjects receiving an ICD-10 diagnosis of psychosis. The kappa for agreement between PSQ positive ratings and comparative measures were ICD-10 criteria derived overall caseness (0.380); PSE/SCAN clinical significance ratings derived overall caseness (0.322); ICD-10 psychosis diagnosis (−0.033); PSE/SCAN clinical significance derived psychosis diagnosis (0.309). The agreement between PSQ ratings and criteria based as well as clinical significance based ratings was therefore generally poor.

5.4. Psychiatric Disorders Specific to Epilepsy: Results from the Neurobehavioral Inventory (NBI) for Epilepsy

NBI total score data were available on 46 subjects, missing values (due to non-completion of sections) being replaced with a zero score in 4/46 subjects. The mean NBI total score on the patients scale was 24.4 and the mean for the carer scale (personal behaviour survey) was 23.1. The median value for both patient and carer scales, was 16.

5.4.1. Agreement between Patient/Carer Ratings on the NBI

The intra-class correlation coefficient between NBI patient and carer scales was 0.76 (significant at the p=0.01 level), thus indicating reasonable agreement between NBI patient and carer scales.

5.4.2. The NBI as a Measure of Generic Psychiatric Caseness

We tested the ability of the NBI patient and carer scales to discriminate psychiatric cases from non-cases, when compared to the gold-standard structured clinical instrument, the CIS-R. CIS-R caseness as previously was decided based on the recommended cut off value of 12 (Lewis, 1992). The total NBI patient score and NBI carer score were compared using Receiver Operating Characteristics Analysis. Figure 14 and Table-15 depict and detail the area under the curve for the NBI patient and carer scales.

Figure 14. ROC Curve comparing NBI patient and carer scales with CIS-R as gold standard in patients with epilepsy.

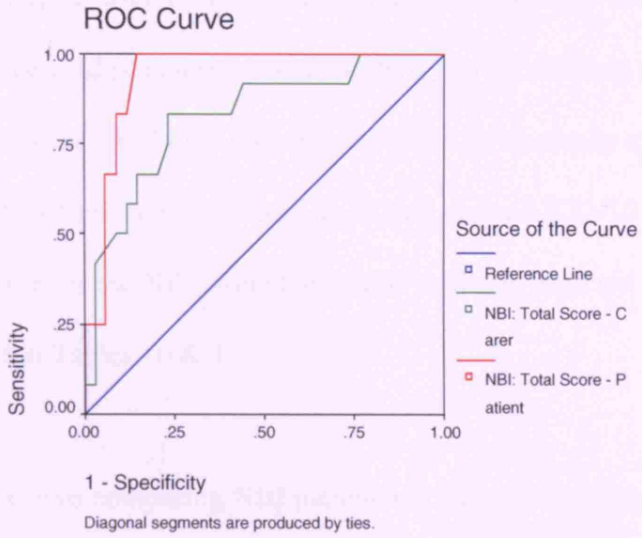
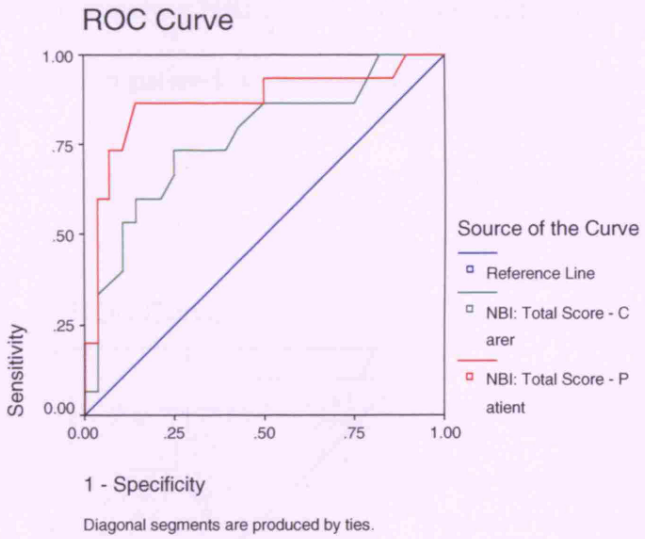


Table 15. Area Under the ROC Curve NBI patient and carer scales vs. CIS-R ≥ 12.

	Area	Std. Error	Asymptotic 95% CI	
Test result variable(s)			Lower bound	Upper bound
NBI: total score – Patient	0.94	0.04	0.87	1.00
NBI: total score – Carer	0.83	0.07	0.69	0.97

We also compared the ability of the NBI patient and carer scales to discriminate psychiatric cases from non-cases, using the ROC analysis and with the PSE/SCAN derived ICD-10 criteria based diagnosis and psychiatric caseness derived through the clinical significance gold standards. Complete NBI and SCAN data was available in 43 individuals. Of these 15 (34.8%) were cases based on clinically significant PSE ratings, and 12 (27.9%) were cases based on SCAN derived ICD-10 diagnosis. The area under the curve for the NBI patient and carer scales is depicted in Figures 15 & 16, and described in Tables 16 & 17.

Figure 15. ROC Curve comparing NBI patient and carer scales with PSE clinically significant symptoms as gold standard in patients with epilepsy.



255Table 16. Area Under the Curve (NBI patient and carer scales vs. PSE Clinical Significance).

	Area Std. Error		Asymptotic 95% confidence interval	
Test result variable(s)			Lower bound	Upper bound
NBI: total score – patient	0.87	0.07	0.74	0.99
NBI: total score – carer	0.77	0.08	0.61	0.92

Figure 16. ROC Curve comparing NBI patient and carer scales with ICD-10 diagnosis as gold standard in patients with epilepsy.

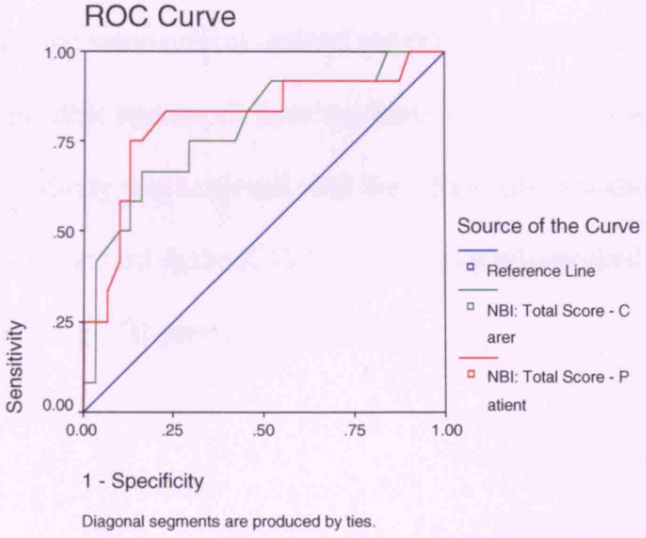


Table 17. Area under the curve (NBI patient and carer scales vs. ICD-10 diagnosis) area under the curve.

	Area Std. Error		Asymptotic Sig.	Asymptotic 95% confidence interval	
Test result variable(s)				Lower bound	Upper bound
NBI: total score – patient	0.82	0.08	.002	0.65	0.98
NBI: total score carer	0.79	0.08	.003	0.63	0.95

5.4.3. Cut off Scores on NBI Patient and Carer Scales

The cut off scores in Table 18 achieved the best match of sensitivity and specificity against CIS-R as also the two gold standards (ICD-10 and clinical significance) adopted for comparison, and represent cut-off points for NBI patient and carer scales. A higher score was required on the patient scale as opposed to the carer scale, in order most effectively to discriminate psychiatric cases and non-cases among patients with epilepsy. However, the same patient optimal cut-off score (32.5) and same carer cut-off score were applicable against all three measures tested. The best match of sensitivity and specificity was achieved with the CIS-R gold standard, followed by PSE symptom gold-standard & the ICD-10 diagnosis gold-standard, with this being most pronounced in the NBI-patient scale ratings.

Table 18. Cut-off values for NBI Patient and Carer scale scores.

Scale	Score (CISR)	Sensitivity (%)	Specificity (%)	Score (PSE)	Sensitivity (%)	Specificity (%)	Score (ICD)	Sensitivity (%)	Specificity (%)
	19/20	100.0	79.4	17/18	86.7	71.4	17/18	83.3	64.5
	25/26	100.0	82.4	24/25	86.7	82.1	24/25	83.3	74.2
NBI-P	32/33	100.0	85.3	32/33	86.7	85.7	32/33	83.3	77.4
	36/37	83.3	88.2	36/37	73.3	89.3	36/37	75.0	83.9
	38/39	83.3	91.2	38/39	73.3	92.9	38/39	75.0	87.1
NBI-C	18/19	83.3	70.6	18/19	73.3	67.9	18/19	75.0	64.5
	19/20	83.3	73.5	19/20	73.3	71.4	19/20	75.0	67.7
	21/22	83.3	76.5	21/22	73.3	75.0	21/22	75.0	71.0
	22/23	75.0	76.5	22/23	66.7	75.0	22/23	66.7	71.0

5.4.4. NBI Patient/Carer Scales: Descriptive Data from the Sub-Scales

We examined the individual NBI sub-scales, both patient/carer ratings. A positive rating on the individual NBI sub-scale was assigned when a score of 3 was exceeded (of a maximum of 5), in line with published recommendations (Blumer, 1995). The results are presented in Table 19.

Table 19: NBI patient and carer-rated symptoms.

NBI Scale	Patient positive (N=46)	Carer positive (N=46)
Writing	6 (13.0%)	4 (8.7%)
Morals	16 (34.8%)	17 (37%)
Religion	6 (13.0%)	3 (6.5%)
Temper	11 (23.9%)	10 (21.7%)
Order	15 (32.6%)	15 (32.6%)
Sex	22 (47.8%)	18 (39.1%)
Fear	12 (26.1%)	13 (28.3%)
Guilt	7 (15.2%)	4 (8.7%)
Seriousness	6 (13.0%)	7 (15.2%)
Sadness	13 (28.3%)	10 (21.7%)
Emotionality	9 (19.6%)	10 (21.7%)
Suspiciousness	3 (6.5%)	8 (17.4%)
Detail	18 (40%)	15 (32.6%)
Cosmic interests	4 (8.7%)	1 (2.2%)
Destiny	4 (8.7%)	3 (6.5%)
Persistence	17 (37.0%)	12 (26.1%)
Hatred	3 (6.5%)	5 (10.9%)
Dependence	8 (17.4%)	8 (17.4%)
Happiness	7 (15.2%)	6 (13%)
Physical/Somatic	17 (37.0%)	19 (41.3%)

5.5. Seizure Severity

All subjects with epilepsy responded to the National Hospital Seizure Severity Scale (NHS3). Subjects and their carers were interviewed with the NHS3 for a maximum of 3 seizures types, each of these being scored on one scale NHS3-I, NHS3-II, and NHS3-III, as well as NHS3-Total Score. All 59 patients with epilepsy as one would expect had at least one seizure type. 44 had only one-seizure type, and a further 15 had a second seizure type. No patient had more than 2 types of seizure.

5.5.1. Descriptive Data on Seizure Severity

The mean NHS3 Type-I (the first type of seizure recorded) score was 12.05 and the mean NHS3 type 2 (the second type of seizure recorded) score was 1.78. The mean NHS3 total score was 13.83. There were no significant differences in mean total scores between males and females (t= −1.69; p= 0.097; 95% CI −5.79 to .49).

5.5.2. Seizure Severity and Psychiatric Caseness

We examined associations between NHS3 type-1, type-2 and total score with the main psychiatric caseness variables using the independent samples t-test. No significant associations between seizure severity and psychiatric caseness as described by PSE-SCAN derived ICD-10 criteria based diagnosis were identified.

We also examined the relationship between seizure severity as measured by the NHS3 and psychiatric caseness as measured by the epilepsy specific measure of

psychopathology, the Neurobehavioral Inventory, both patient and carer versions, with the revised cut-off scores (33 and 21 respectively) identified by us. No significant associations between seizure severity scores and epilepsy specific psychopathology either patient or carer rated were observed. The results are described in Table 20.

Table 20: Independent samples t-test comparing seizure severity and psychiatric caseness across measures

Scale				*CI*		
	t	df	Sig.	Mean Diff.	Lower	Upper
CIS-R						
NHS3-Type1	0.13	19.69	0.898	0.25	-3.61	4.10
NHS3-Type 2	-2.08	18.20	0.05	-2.98	-5.99	3.53
NHS3-total score	-1.37	20.80	0.19	-2.73	-6.88	1.42
NBI Patient						
NHS3- Type 1	-0.25	18.49	0.81	-0.49	-4.58	3.59
NHS3 Type 2	-1.29	16.37	0.21	-1.79	-4.71	1.14
NHS3- total score	-1.01	17.32	0.33	-2.28	-7.04	2.48
NBI Carer						
NHS3 Type 1	0.09	32.36	0.92	0.15	-3.29	3.60
NHS3 Type 2	-0.97	24.47	0.34	-1.17	-3.67	1.33
NHS3- total score	-0.52	28.51	0.61	-1.02	-5.05	3.02

5.6. Disablement in Patients with Epilepsy

Disablement was estimated in 53 of 59 patients (89.8%) with epilepsy using the Subjective Handicap in Epilepsy scale. This scale has six sub-scales measuring work; social & personal; physical; self-perception; life-satisfaction and change domains. Higher scores indicate lower levels of disablement. Table 21 provides descriptive data of SHE subscales.

Table 21. SHE – Descriptive data.

	Work	Social & personal	Physical	Self perception	Life satisfaction	Change
Mean	68.6	80.3	61.8	66.3	65.0	53.9
Std. Error of Mean	3.8	3.7	3.5	3.9	3.4	2.3
Median	75.0	94.0	65.0	70.0	69.0	54.0
Mode	100.0	100	56.0	100.0	56.0	50.0
Std. Deviation	27.5	27.0	25.7	28.6	24.6	16.9
Minimum	3.12	6.25	0.00	0.00	0.00	14.28
Maximum	100.00	100.00	100.00	100.00	100.00	100.00

5.6.1. Psychiatric Co-morbidity and Disablement

We examined the relationship between psychiatric caseness as determined by ICD-10 criteria following SCAN interview and disablement in epilepsy. Patients with a diagnosable psychiatric disorder had significantly greater disablement as measured on the "social & personal", "physical", and "life satisfaction" subscales of the SHE, and approached significance on the "self perception" scale of the SHE. The change subscale of the SHE was also significantly associated with ICD-10 psychiatric diagnosis. There were however no associations between the "work" subscale and ICD-10 psychiatric diagnosis. Table 22 has the details.

Table 22. Independent Samples Test comparing ICD-10 psychiatric diagnosis with disablement

	T	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% CI	
						Lower	Upper
She work	1.75	46.0	0.09	14.83	8.48	−2.24	31.91
She social/personal	2.38	20.94	0.03	21.96	9.23	2.76	41.16
She physical	3.52	24.91	0.002	26.49	7.52	11.00	41.97
She self perception	1.93	46.0	0.06	17.55	9.07	−0.72	35.81
She life satisfaction	3.98	27.93	0.001	27.41	6.88	13.31	41.51
She change	2.52	21.67	0.02	14.45	5.74	2.53	26.36

As patients with epilepsy often fail to meet conventional diagnostic criteria, while suffering from disabling psychiatric symptoms (Krishnamoorthy, 2002a), we compared scores on the SHE subscales with psychiatric caseness on the symptom based measure, the CIS-R, assuming the recommended cut-off score of 12. CIS-R caseness was significantly associated with all sub-scales of the SHE (Table 23). We also examined epilepsy specific psychopathology as defined by the NBI. NBI-Patient total score (>20) caseness was significantly associated with all sub-scales except SHE-Work and SHE-Change. Caseness as defined by the revised NBI patient cut-off score (>38.5) was associated with "social & personal, physical & change" but not with "work, self-perception & life-satisfaction". On the other hand, caseness as defined by the NBI total carer scale score was associated with "social & personal, physical and life satisfaction" sub-scales, but not work, self-perception and change sub-scales.

Table 23. Comparisons of SHE & CIS-R caseness.

	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% CI	
						Lower	Upper
Work	2.7	19.8	0.01	22.9	8.4	5.3	40.5
Social/personal	4.0	15.8	0.001	35.1	8.7	16.6	53.6
Physical	5.0	22.4	0.001	32.6	6.6	19.0	46.2
Self perception	2.6	16.5	0.019	25.8	9.9	4.9	46.8
Life satisfaction	3.8	19.0	0.001	27.3	7.3	12.1	42.6
Change	3.2	18.0	0.005	17.37	5.3	6.1	28.5

5.6.2. Seizure Severity & Disablement

We tested for associations between seizure severity and disablement scores using spearman correlations. Correlations were generally stronger among those with two seizure types rather than one seizure type only. The NHS3 total score was significantly correlated with all SHE scales except the "work" scale where it approached but failed to achieve significance. The results are described in Table 24.

Table 24. Correlations between scales for seizure severity and disablement.

		Work	Social/ Personal	Physical	Self perception	Life satisfaction	Change
NHS3 – one seizure type	Spearman Correlation	−0.8	−0.2	−0.1	−0.3	−0.3	−0.2
	Sig. (2-tailed)	0.6	0.3	0.54	0.06	0.07	0.3
NHS3 – two seizure types	Spearman Correlation	−0.3	−0.3	−0.4	−0.3	−0.3	−0.3
	Sig. (2-tailed)	.0.01	0.01	0.01	0.05	0.002	0.03
NHS3 – total score	Spearman Correlation	−0.3	−0.3	−0.3	−0.4	−0.5	−0.3
	Sig. (2-tailed)	0.08	0.04	0.01	0.01	0.001	0.03

5.7. The Relative Contributions of Seizure Severity and Psychiatric Co-morbidity to Disablement in Epilepsy

A well-established association between seizure severity and disablement in epilepsy exists (Baker, 1996). However, while disablement has been demonstrated in many psychiatric disorders, there are few studies that have examined the contribution of co-morbid psychopathology to disablement in epilepsy (Baker, 1996 for example). Having examined associations between seizure severity and disablement, psychiatric caseness and disablement, and seizure severity and psychiatric caseness, we proceeded to examine post-hoc, the relative contributions of seizure severity and psychiatric co-morbidity to disablement in epilepsy.

Generalised Linear Modelling in SPSS (GLM-SPSS) was used to test this hypothesis in all patients with epilepsy in whom NHS3, SHE, PSE "clinical significance" and ICD-10 data were available (49 subjects).

Each of the SHE scales were in turn selected as the dependent variable, with sex being the fixed factor in all instances. Age, rating of caseness on "clinical significance" and ICD-10 criteria were entered as covariates in this model.

5.7.1. Clinical Significance, ICD-10 Diagnosis, Seizure Severity & Subjective Handicap

For each of the SHE scales, psychiatric co-morbidity accounted for the greatest proportion of shared variance, when compared to the other covariates in the model,

seizure severity (NHS3) total score and sex. Further, once the proportion of variance explained by the psychiatric co-morbidity variable had been accounted for, previously demonstrated associations between seizure severity total score and disablement (Table 25) were no longer significant in some instances. Thus "Clinical Significance" explained the greatest proportion of the shared variance when compared with seizure severity, age and sex. While the physical and self-perception subscales of the SHE were also influenced by seizure severity and showed a significant association in this regard, here too the impact of co-morbid psychiatric disorder appeared greater. The work sub-scale of the SHE was alone not affected either by seizure severity or co-morbid psychopathology.

When ICD-10 ratings of psychiatric caseness were entered into the GLM equation as the measure of psychiatric caseness, the results were similar. Once again, the work subscale of SHE was not affected either by seizure severity of psychiatric co-morbidity. ICD-10 diagnosis explained the greatest proportion of the shared variance for other sub-scales, except the self-perception sub-scale in which seizure severity appeared to explain a greater proportion of the shared variance. The change subscale of the SHE also did not follow prediction in this instance, with sex accounting for the greatest proportion of shared variance with regard to this subscale.

Tables 25 and 26 have details of the F values, eta-square values and significance ratings of these associations.

Table 25. GLM-SPSS comparing "Clinical Significance" rating with NHS3 & SHE scales.

SHE – Work	Sex	NHS3	Age	"CS"
F value	1.4	2.2	0.3	2.5
Partial Eta Squared	0.03	0.05	0.01	0.05
Significance	0.3	0.2	0.6	0.1
SHE – Social/Personal				
F value	2.7	3.7	6.7	17.2
Partial Eta Squared	0.06	0.08	0.13	0.28
Significance	0.1	0.1	0.01	.001
SHE – Physical				
F value	0.7	4.9	1.2	8.2
Partial Eta Squared	0.01	0.10	0.03	0.16
Significance	0.43	0.03	0.3	0.01
SHE – Self perception				
F value	3.5	5.6	0.7	7.5
Partial Eta Squared	0.07	0.11	0.02	0.15
Significance	0.07	0.02	0.39	0.01
SHE – Life satisfaction				
F value	0.1	4.2	0.2	9.7
Partial Eta Squared	0.002	0.09	0.005	0.18
Significance	0.76	0.05	0.63	0.003

SHE – Change				
F value	0.3	1.5	2.9	7.0
Partial Eta Squared	0.01	0.03	0.06	0.14
Significance	0.59	0.23	0.09	0.01

Table 26. GLM-SPSS comparing ICD-10 diagnosis with NHS3/SHE scales.

SHE- Work	Sex	NHS3	Age	ICD-10
F Value	1.3	2.7	0.2	2.4
Partial Eta Squared	0.03	0.09	0.003	0.05
Significance	0.25	0.11	0.70	0.13
SHE- Social & Personal				
F Value	2.7	5.9	3.5	6.8
Partial Eta Squared	0.09	0.12	0.07	0.13
Significance	0.11	0.02	0.07	0.01
SHE- Physical				
F Value	0.55	5.93	1.2	13.1
Partial Eta Squared	0.01	0.12	0.03	0.23
Significance	0.46	0.02	0.29	0.001
SHE- Self Perception				
F Value	3.6	7.4	0.3	4.3

Partial Eta Squared	0.08	0.14	0.01	0.09
Significance	0.07	0.01	0.60	0.05
SHE- Life Satisfaction				
F Value	0.1	5.41	0.1	10.6
Partial Eta Squared	0.002	0.11	0.002	0.2
Significance	0.78	0.03	0.78	0.002
SHE- Change				
F Value	0.24	2.3	2.1	5.1
Partial Eta Squared	0.01	0.05	0.05	0.01
Significance	0.62	0.14	0.16	0.03

The aforementioned results were replicated with the CIS-R and NBI- Patients Total Score, both these variables emerging as more significant predictors of disablement when compared to seizure severity scale scores. However, the NBI-Carer total score failed to demonstrate similarly significant associations with either SHE or NHS3 scores.

5.8. Summary of Results from the Primary Care Study

The primary care study demonstrated clearly that psychiatric co-morbidity was over-represented in persons with epilepsy when compared with population-based controls in the overall sample, although the differences narrowly missed achieving significance in the paired samples t-test. Core symptoms of common mental disorder, worry, depression and anxiety etc., were significantly more common in the epilepsy

group. These differences between cases and controls were generally reflected across the screening and diagnostic measures.

The screening measures generally compared well with the diagnostic measures. ROC analysis was used to derive the cut off scores on each measure, both in epilepsy and in control groups, simultaneously optimising sensitivity and specificity.

In depth analysis of the SCAN data in the epilepsy group revealed that CMD symptoms were most common in these patients.

Both the CIS-R and the NBI appeared to perform well as measures of overall psychiatric caseness, and performed comparably against both the PSE-based gold standards used, ICD-10 diagnosis and clinical significance ratings. Revised cut-off scores for these instruments representing the optimal sensitivity and specificity are presented. The psychosis symptom questionnaire did not however perform well in comparison to both gold standards.

We did not find any evidence for associations between seizure severity (NHS3) and psychiatric co-morbidity either generic (diagnosed in SCAN interview) or specific to epilepsy (NBI). Psychiatric co-morbidity, however measured was significantly associated with disablement among people with epilepsy. This was true for all sub-scales of the SHE except the work subscale. Seizure severity (NHS3) was also associated with disablement (SHE) overall, except the work subscale. Using GLM-SPSS, we found psychiatric co-morbidity to be strongly associated with

subjective handicap, and once this had been accounted for, the associations between seizure severity and subjective handicap became largely irrelevant.

The implications of these findings will be addressed in some detail in the discussion section.

6. STUDY-II:

PREVALENCE, PATTERNS AND ASSESSMENT OF PSYCHIATRIC CO-MORBIDITY IN AN INSTITUTION FOR EPILEPSY

6.1. Background and Rationale to the Present Study

While a number of studies have examined co-morbidity between learning disability (LD) and epilepsy, and LD and psychiatric disorder, in hospital, institutional and community-based populations; the literature on neuropsychiatric epidemiology at this important interface between epilepsy and LD remains rather scant. A detailed review of available literature is presented in the review sections of this thesis (section 3.3) and reveals a number of lacunae in the available literature.

Specifically, a number of the studies have:

(1) Used generic measures that have not been specifically developed either for use in epilepsy populations, or learning disability populations, or indeed in populations where epilepsy and learning disability are co-morbid.

(2) Failed to rate carer/observer information systematically using valid measures, carer/observer ratings being an important source of information in these populations, limited as they may be in their ability to share health related information adequately and accurately.

(3) Failed to differentiate between psychiatric co-morbidity that is generic, and psychiatric co-morbidity that is specific to either epilepsy, or learning disability, or the co-morbidity thereof.

There are relatively few psychiatric outcome measures designed to assess the subject with acquired cognitive impairment or learning disability (Kerr, 1997). Further, as

measurement within learning disability (and dementia) is often indirect, with reliance being placed on caregiver or observer reports, the reporting of outcomes is often influenced by the caregiver (Espie, 1997). Given that clinical experience indicates even cognitively unimpaired subjects with intractable epilepsy under-report psychopathology (particularly of the ictal variety), carer reports are an essential element of the measurement of psychiatric outcome.

Improved management methods, changing attitudes to epilepsy, and the progressive closure of institutions in the western world in the past three decades or more, have resulted in people with epilepsy no longer being admitted to institutions, for epilepsy alone. Indeed, institutionalisation today is most often for younger moderate to severely learning disabled people with intractable epilepsy, and often with significant concomitant behavioural problems (Espie, 1997). Thus the vast majority of adults with severe refractory epilepsy are resident in the community (with or without support), and those who reside in institutions are housed in that setting mainly because of co-morbid learning disability, psychiatric disorder or both. The opportunity in this generation to study adults resident in an institution for epilepsy, with the primary reason for their residence in that setting being intractable epilepsy, is thus no longer common place. The National Society for Epilepsy- Centre for Epilepsy, in Chalfont St. Peter, Buckinghamshire, a few miles outside Greater London, is unique in this respect.

The NSE centre houses nearly 300 people with intractable epilepsy at any one time. About 10% of these are individuals with epilepsy normally resident in the community or other residential care settings, attending the assessment unit within the

centre, for periods usually between one and eight weeks to undergo a detailed evaluation. A further 15–20% (45–60 individuals) are in various rehabilitation programmes, projects that encourage progress into supported or independent living and in many cases eventual return to the community.

The majority of residents (over 70%) have been housed in the centre for the long term, in many cases (especially older residents) for decades. Long-term residents are spread out among 14 houses that offer individual rooms for residents with shared facilities. The placement of individual cases is dependent to some extent on the level of disability (physical or behavioural), some houses being better equipped to deal with greater disability than others, for staffing, facilities and other logistic reasons. Each house has a team of care workers lead by a house manager. One component of the rehabilitation program, a supported living project for those progressing to independent living, consists of apartments that residents share with nominal support from carers.

Until the beginning of this study in October 1998, psychiatric care at the NSE was largely informal, and provided as part of the neuropsychiatry assessment service from the National Hospital for Neurology and Neurosurgery in London. The reporting of an increased burden of behavioural problems by the staff at the centre, and the felt need for a formal psychiatric service led to the director of the NSE centre commissioning a formal review of mental health service needs, thus providing the opportunity to survey this population.

The institutional study reported herein was therefore established with the following aims.

6.2. Aims

To survey residents at the NSE Centre for Epilepsy, Chalfont St.Peter, to determine:

(1) The prevalence and patterns of psychiatric co-morbidity in this population;

(2) Compare responses to instruments of psychiatric research that assess psychiatric co-morbidity using different sources of information: the patient himself, the informed/ expert observer; and the caregiver;

(3) To assess both generic and epilepsy specific domains of psychopathology in this population;

(4) To study the ability of these different measures to identify psychiatric caseness, when compared to the gold-standards of ICD-10 diagnosis "clinical significance";

(5) To estimate mental health needs in this population.

Aims 1–4 are central to the objective of this thesis and the results of these investigations are described in detail. Aim 5 formed the service component of the review, and has been presented as a formal report to the National Society for Epilepsy.

6.3. Methods

6.3.1. Setting

The National Society for Epilepsy- Centre for Epilepsy, Chalfont St. Peter, Buckinghamshire, UK.

6.3.2. Participants

All people with epilepsy resident at the centre during the study period (October 1998 to September 1999) were included in the survey. People with epilepsy attending the assessment unit were excluded, as they would largely have been unrepresentative of this population. People with epilepsy in various rehabilitation programmes were however included, as they were long term residents, staying at least one year at the centre (thus representative populations in residential care), and contributed to the mental health service needs at the centre.

There were 272 long-term residents in the centre database at the time of commencement of the study. Full medical records could be obtained for 261 (96%) of these residents. Seventeen of these 261 residents (henceforth referred to as cases) could not be located subsequently due to logistic problems such as resident movement (house transfers) within the centre, resident leaving the centre during the course of the study etc. A further sixteen refused consent to be interviewed and assessed in person. 228 of 261 cases (87%) were recruited to participate in the interview and assessment components of the study.

6.3.3. Measures

6.3.3.1. Review of Case Records & Interview with Professional Caregiver

The case notes of all residents were systematically reviewed for mental health problems, and a report from the house manger on each resident was sought. The professional caregiver interviewed had to have known the person with epilepsy for at least one year. Professional caregivers chosen in this way also completed the Neuropsychiatric Inventory (NPI) (Cummings, 1994) a carer rated measure of behavioural dysfunction in neurological disorders with the research assistant. The NPI (reviewed in greater detail subsequently) is a widely used measure in a number of conditions and has been demonstrated to have good psychometric properties in neurological populations (Aarsland, 1999; Diaz-Olivierretta, 1999; Litvan, 1998).

6.3.3.2. Interviews with Persons with Epilepsy

Cases who consented to being personally interviewed by the research assistant (an experienced mental health professional) were first assessed using the Mini-Mental State Examination (Folstein, 1975). Based on the MMSE scores they were classified as cognitively impaired (<24) or cognitively unimpaired subgroups (≥ 24). This was done as assessments of cognitive status were not available in all cases, and when available were not necessarily current.

Cases underwent a general interview about their health, psychological and social well being with the RA over a 30-min. period, and were rated on the Brief

Psychiatric Rating Scale (Overall & Gorham, 1962), a valid and reliable observer rated measure of psychopathology in psychiatry settings (reviewed in greater detail below).

Cases who on the basis of the aforementioned assessments were considered suitable for an in-depth psychiatric interview (not cognitively impaired and able to respond adequately to questions in interview), and who consented to take part in the same, were interviewed in phase II by this candidate, using the Present State Examination (PSE) components of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (WHO, 1992b). The computer version for WINDOWS was used for this purpose (WHO, 1995), and an ICD-10 diagnosis generated based on the SCAN algorithms. The PSE components of the SCAN were used in this study, sections 2–12 of PSE (section I) being completed, as also section 14 (screen for PSE-section 2). A rating of "clinical significance" was also made by the candidate, an experienced neuropsychiatrist, based on the responses to each domain of the PSE. A patient was rated to have a clinically significant mental disorder, if they had 3 more symptoms that were disabling in that domain of the PSE. The rational for this strategy, which has been adopted in major international studies has been addressed in the previous section. As psychiatric co-morbidity in epilepsy is believed not to follow conventional descriptions and criteria, it was felt that such an operationalised clinician rating of caseness was necessary, in order to make effective comparisons between instruments.

6.3.3.3. Other Measures

Cases judged to be suitable for phase II were also requested to complete the patient sections of the Neurobehavioral Inventory (NBI) (Blumer, 1995), described in detail in section 4, with the named professional caregiver for each case being asked to complete the caregiver section of this instrument. This was done in order to assess psychiatric co-morbidity specific to epilepsy in this population, and to compare this generic psychiatric disorder as rated on SCAN, and caregiver as well as observer ratings of psychiatric co-morbidity on the NPI and BPRS respectively.

6.3.4. Review of NPI & BPRS

6.3.4.1 Neuropsychiatric Inventory (NPI)

The NPI (Cummings, 1994) was developed to assess a wide range of behaviours encountered in dementia patients, to provide a means of distinguishing frequency and severity of behavioural changes and to facilitate rapid behavioural assessment through the use of screening questions. The behavioural domains to be assessed were chosen after a careful review of the literature occurring in different dementias and preliminary studies of behavioural changes in patients with vascular dementia and fronto-temporal dementia. Ten behavioural domains are evaluated by the NPI: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor behaviour. Each behavioural domain is explored with a caregiver who has at least daily contact with the patient, with a screening question, which if the caregiver answers in the affirmative is followed up by

a series of questions relevant to behaviours in that domain. Each abnormal behaviour identified is rated on severity (1=mild; 2= moderate; 3= severe) and frequency (1= occasionally, less than once a week; 2= often, about once a week; 3= frequently, several times a week; 4= very frequently, once or more per day or continuously).

Cummings (1994) reports the psychometric properties of this (then) new scale. Content validity was assessed by a Delphi panel of ten international experts, each of whom rated each question between 1 (well assessed) and 4 (poorly assessed). Concurrent validity was assessed with respect to BEHAVE-AD (Reisberg, 1987) and HDRS (HDRS, 1967). The delusions, hallucinations, dysphoria, anxiety, agitation/aggression, and aberrant motor behaviour subscales of the NPI were compared with delusions, hallucinations, affective disturbances, anxiety and phobias, aggressiveness, and activity disturbances subscales of the BEHAVE-AD; the dysphoria subscale of NPI with the HDRS. Between rater reliability was assessed by a team of qualified raters in 45 patients/caregivers. Test-retest reliability was determined by conducting a second caregiver interview within 3 weeks of the initial interview, this being performed in 20 caregivers by a different clinician. Forty caregivers of non-demented control subjects were also interviewed.

Spearman's correlations were assessed to compare NPI subscale scores and the BEHAVE-AD subscale and HDRS scores. Cronbach's coefficient alpha was determined to assess internal consistency; reliability and Pearson's correlations were calculated for the item-independence study.

The authors report that (Cummings, 1994):

- The screening questions were judged to have an acceptable false positivity and false negativity rate.
- Content validity as judged by the Delphi panel was good, the troublesome behaviour alone being reformulated as "aberrant motor behaviour".
- All NPI items were expressed throughout the population surveyed the scores in general being low. Apathy was the most frequent behaviour expressed, and euphoria the least frequent.
- Good concurrent validity was established with NPI items correlating generally well with BEHAVE-AD and HDRS scales. The dysphoria subscale alone correlated less well (but adequately) with both the above scales.
- Internal consistency of the NPI for both frequency and severity was good, a Cronbach's Alpha Score of between 0.87 and 0.88 for all scales overall
- Between rater reliability was very high and test-retest reliability correlations were for 0.79; p= 0.0001 (frequency) and 0.89; p=0.0001 (severity).

The results establish the NPI as an instrument in which the clinician can have confidence as a means of assessing and quantitating behavioural changes in dementia (Cummings, 1994).

The NPI has been used widely to study patients with dementia, as well as a number of conditions in which cognition can be impaired to varying degrees, including Parkinson's disease (Aarsland, 1999), multiple sclerosis (Diaz-Olavarietta, 1999), cortico-basal degeneration and progressive supranuclear palsy (Litvan, 1998) etc. The instrument is also in use for the differential analysis of behaviours in

dementia and as an outcome measure in trials of drugs used in the treatment of dementia[22]. However, there are no published reports examining the psychometric properties of the NPI in populations with epilepsy.

6.3.4.2. Brief Psychiatric Rating Scale (BPRS)

One of the more commonly used interview rating scales is the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). To use the BPRS, the mental health professional completes a mental status interview with the patient and then rates that patient on a series of 18 psychiatric symptoms such as motor retardation, blunted affect, conceptual disorganization, anxiety, and guilt. Expanded definitions of each of these terms are provided to the examiner. The interviewer rates each domain on a seven-point Likert scale from "not present," the lowest rating, to "extremely severe," the highest rating. An experienced interviewer can complete the ratings in 2/3 minutes. The BPRS has been used extensively in drug-outcome and other studies. The advantage of the BPRS is that the inter-rater reliability is reasonably high for a rating scale of this nature. A summary of over 300 studies using the BPRS found an inter-rater reliability correlative of .80 or above on the total score in most studies (Sadock, 2004).

Originally the scale had 16 items to which two items were then added, the BPRS-18. Factor analysis has shown that the items of the BPRS-18 can be grouped in clusters or factors, each comprising a set of items that correlate highly among themselves, but associate little with the remaining items (Czobor, 1996).

Benefits of the BPRS:

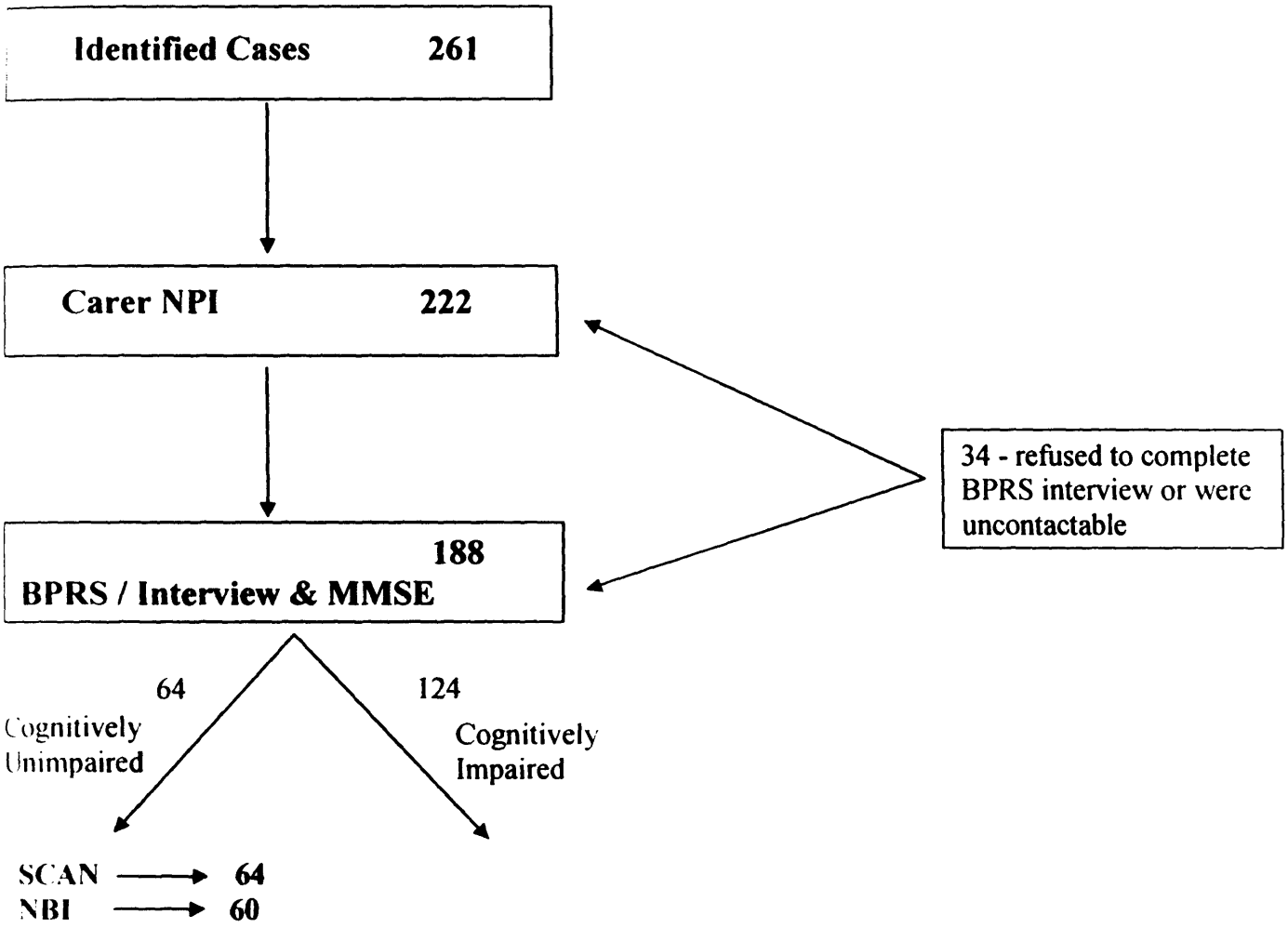
- Well established – among the most researched instruments used in psychiatry
- Well known – clinicians tend to be familiar with symptom scores and changes
- Sensitive to change – may be used to rate treatment response
- Broad evaluation – allows rating of severity of a number of different symptoms
- Used in many classic studies of new anti-psychotics
- Psychometric properties and underlying factor structure is well-established
- Grouping on item scores allow scoring on distinct factors (tension; emotional withdrawal; mannerisms and posturing; motor retardation; uncooperativeness)

Challenges of the BPRS:

- Limited in scope - focus on positive and general psychopathology. Does not focus on negative symptoms. Needs to be utilised in combination with a negative symptom assessment tool, if negative symptomatology is to be captured
- Ambiguous interpretation - there are several ways symptoms are reported (eg., on a scale of 0–6 or a scale of 1–7); the dual reporting scale must be taken into consideration when interpreting scores
- Use of 1–7 scale – the non-linearity into the scale can complicate interpretation changes over time, particular with regards to response rates
- Examiner subjectivity
- Examiners can only rate what they observe during interview

A Synopsis of study methods in flow chart form is presented below.

Study II : Residential Care



6.3.5. Analysis

Data was analysed using SPSS for WINDOWS (version 10.0). Descriptive statistics were examined using the frequencies and descriptives functions of SPSS. Both parametric and non-parametric correlations between NPI and BPRS total scores and sub-scale scores were examined as appropriate (Pearson, Spearman and Kendall's Tau values as appropriate being obtained). ROC analysis (Section 4.8.2; pg. 178) was carried out to compare the case-finding abilities of the different scales against the ICD-10and clinical significance gold standards.

A technique employed in the institutional study and not the primary care study was Factor Analysis.

Factor Analysis (FA) and Principal Components Analysis (PCA):
The goal of these techniques is to examine the structure of the relationship between variables and not to see how they relate to other variables, such as group membership or a set of dependant variables. These techniques are therefore used

(1) To explore the relationship among variables

(2) To see if the pattern of results can be explained by a smaller number of underlying constructs (sometimes called latent variables or factors)

(3) Test some hypothesis about the data

(4) Reduce the number of variables to a more manageable size

PCA is currently used as the first step in FA. One purpose of the PCA and FA is to determine if numerous measures (paper and pencil tests, individual items on tests, physical characteristics or other measures) can be explained on the basis of a smaller number of factors. Factor analysis may thus be confirmatory (to confirm a hypothesis that the results of 15 different tests can be explained by three factors for example) or exploratory (when it is not known how many factors exist).

Whether variables are unique or not is measured in this technique, by measuring the converse of uniqueness, what is called the communality of a variable. The communality of a variable can be approximated by its multiple correlation, R^2, with all of the other variables: that is, how much it has in common with them and can be predicted by them. The uniqueness of an index variable (variable-1 for example) is $1-R^2$; that portion of variable 1 that cannot be predicted by (i.e., is unrelated to) the remaining variables. (Norman and Streiner, 2000).

6.4. Results

6.4.1. Descriptive Data

228 persons with epilepsy were recruited; of these 164 (71.9%) were men and 64 (28.1%) women. 67 persons with epilepsy (25.7% of the total population) had previously identified psychiatric problems that required consultation with a mental health professional. The broad classification and frequency of these problems as described in the records is detailed in Table 27.

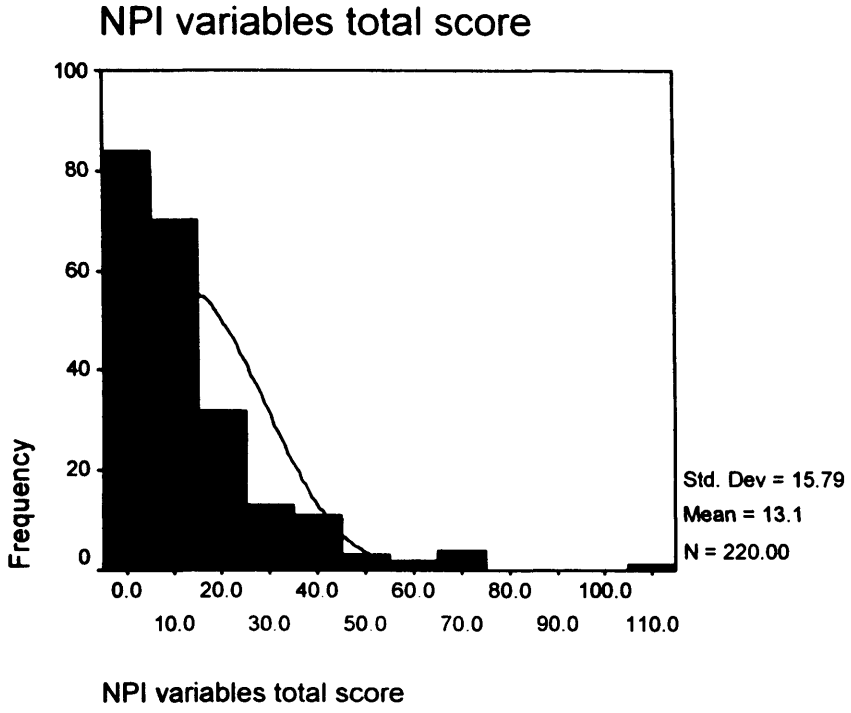
Table 27. Psychiatric co-morbidity as reported in clinical case-notes.

Diagnosis	Cases	Percent
Total	67	25.67%
Psychosis	19	7.2%
Depression	17	6.5%
Aggression	10	3.8%
Behavioural problems	5	1.9%
Other neurotic disorder	5	1.9%
Dementia	6	2.2%
Bipolar disorder	1	0.38%
Alcohol dependence	1	0.38%
Personality disorder	1	0.38%
Unspecified	2	0.76%

6.4.2. Descriptive Data from the Neuropsychiatric Inventory (NPI)

Completed NPI data was available for 222 of 228 subjects (85.1%), as reliable professional carers who had contact with the individual for at least one year could not be identified for a further six subjects. The mean NPI score was 13.1, the median score 8, with a standard deviation of 15.8 and range from 0 to 108. The histogram below shows the distribution of scores (Fig. 17).

Figure 17.: Histogram showing distribution of the NPI variables total score.



6.4.3. Factor Analysis of the NPI – Performance as a Carer Rated Measure for Epilepsy

As the psychometric properties of the NPI have not been assessed in populations with epilepsy, we examined the internal consistency and factor structure of this measure. The internal consistency of the total NPI scores was calculated from the individual NPI sub-scale scores; the scale demonstrated good internal consistency (Cronbach's $\alpha = 0.76$). A principal components analysis (PCA) with varimax rotation was then performed on the NPI sub-scale data. Table 5 presents the communalities and factor loadings of the variables, plus the Eigen values and percentage of variance accounted for by each factor. Four factors with an Eigen value greater than 1 were extracted,

accounting for 58.8% of the total variance. Communalities were generally satisfactory (range 0.5–0.7). Relatively low communalities were found for the apathy (0.35) and delusions (0.39) variables.

An examination of the factor loadings in table-28 suggests that the PCA produced an interpretable factor matrix. Factor 1, which accounts for 28.4% of the total scale variance, has relatively high loadings for NPI delusions, hallucinations, motor disturbance and sleep disturbance; Factor 1 was interpreted as a psychosis factor. Factor 2, which accounts for 11.8% of the total scale variance, has relatively high loadings for agitation, apathy, disinhibition and irritability. This suggests that factor 2 might represent an inter-ictal dysphoric disorder factor. Factor 3, which accounts for 10.1% of the total scale variance, has relatively high loadings for depression and appetite change. This factor was interpreted as a depression factor. Finally, factor 4, which accounted for 8.5% of the total scale variance, has relatively high loadings for anxiety and euphoria. We interpreted this as an anxiety factor.

Table 28. Factor loadings, communalities, Eigen values and percentages of variance for PCA of NPI sub-scale data.

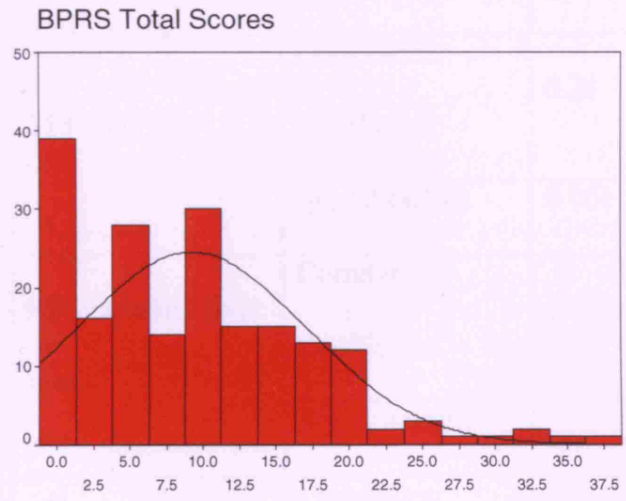
NPI Sub-scale	Factor 1 (Psychosis)	Factor 2 (IDD)	Factor 3 (Depression)	Factor 4 (Anxiety)	Communality
Delusions	0.45				0.39
Hallucinations	0.80				0.70
Motor disturbance	0.73				0.58
Sleep disturbance	0.60		0.41		0.56
Agitation		0.80			0.72
Apathy		0.46			0.35
Disinhibition		0.55			0.49
Irritability		0.83			0.70
Depression			0.75		0.60
Appetite change			0.66		0.57
Anxiety				0.75	0.71
Euphoria				0.77	0.70
Eigen value	3.41	1.42	1.21	1.02	
% of variance	3.41	1.42	1.21	1.02	

6.4.4. Descriptive Data from the Brief Psychiatric Rating Scale (BPRS)

Completed BPRS data was available in 188 of 261 subjects (70%), a further 40 subjects failing to complete the 30 minute interview with the research assistant, for a variety of reasons (refusal when contacted, premature termination, inadequate information available for BPRS ratings etc.).

The mean BPRS score was 20.4, with a standard deviation of 39.4 and range from 0–162. Fig. 18 describes the distribution of BPRS scores.

Figure 18. Histogram showing the distribution of the BPRS scores.



6.4.5. Comparison of Carer/Expert-Observer Rated Instruments (NPI and BPRS)

We examined non-parametric correlations between NPI (caregiver rated psychiatric co-morbidity) and BPRS (observer rated psychiatric co-morbidity) total scores. NPI and BPRS total scores were correlated with one another, albeit somewhat weakly. The results are expressed in Table 29.

Table 29. Non-parametric correlations between NPI and BPRS total scores.

			NPI variables total score	BPRSTOTL
Kendall's tau_b	NPI variables total score	Correlation Coefficient	1.000	0.21
		Sig. (2-tailed)		0.001
	BPRSTOTL	Correlation Coefficient	0.21	1.000
		Sig. (2-tailed)	0.001	
Spearman's rho	NPI variables total score	Correlation Coefficient	1.000	0.30
		Sig. (2-tailed)		0.001
	BPRSTOTL	Correlation Coefficient	0.30	1.000
		Sig. (2-tailed)	0.001	

6.4.6. Correlations between NPI and BPRS Subscales

We examined correlations between NPI and BPRS subscales. In general NPI and BPRS subscales appeared to correlate poorly. Those subscales for which a correlation coefficient (Spearman's Rho) of 0.2 or higher were found are summarized below.

1. NPI Delusions: Not correlated with any BPRS items
2. NPI Hallucinations: BPRS Anxiety- 0.20: BPRS Guilt- 0.25; BPRS Unusual thought content- 0.23
3. NPI Agitation: BPRS conceptual disorganisation- 0.22; BPRS Tension- 0.21; BPRS mannerisms and posturing- 0.21; BPRS hostility- 0.20; BPRS hallucinations- 0.21; BPRS uncooperativeness- 0.20; BPRS unusual thought content- 0.22; BPRS disorientation- 0.23
4. NPI Depression/ dysphoria: BPRS emotional withdrawal- 0.24; BPRS guilt feelings- 0.21; BPRS depressed mood- 0.26; BPRS hostility- 0.24; BPRS uncooperativeness- 0.23
5. NPI Anxiety: BPRS anxiety 0.18
6. NPI Euphoria/Elation: BPRS unusual thought content- 0.20
7. NPI Apathy/indifference: BPRS emotional withdrawal 0.23; BPRS unusual thought content- 0.22
8. NPI Disinhibition: Not correlated with any BPRS items
9. NPI Irritability/Lability: BPRS tension- 0.20; BPRS hostility- 0.27; BPRS hallucinatory behaviour- 0.22
10. NPI aberrant motor behaviour: BPRS tension- 0.22; BPRS uncooperativeness- 0.24; BPRS blunted affect- 0.20

11. NPI aberrant sleep behaviour: BPRS mannerisms and posturing- 0.23; BPRS grandiosity- 0.30; BPRS hostility- 0.25; BPRS uncooperativeness- 0.20
12. NPI- appetite/eating change: Not correlated with any BPRS items

6.4.7. NPI & BPRS Comparisons in Cognitively Impaired and Cognitively Unimpaired Populations

There were no differences between cognitively impaired and cognitively unimpaired populations in terms of age (t=0.388; p=0.699; CI= -3.6 to 5.3) or sex (chi square=0.074; p=0.786).

MMSE, NPI and BPRS data was available in 188 persons with epilepsy. 64 of these individuals (34%) scored 24 or more on the MMSE, and were judged not to be cognitively impaired. The remaining 124 (66%) were judged to have cognitive impairment.

We used the independent samples t-test to compare NPI and BPRS total scores in the cognitively impaired and non-cognitively impaired groups of patients with epilepsy. Both BPRS and NPI total scores were significantly elevated in the cognitively impaired group, the difference being statistically significant, more so with BPRS than with NPI (table-30).

Table 30. Independent samples *t*-test comparing NPI and BPRS total scores in cognitively impaired and non-cognitively impaired groups.

	t	df	Sig. (2-tailed)	Mean Difference	Std. Error	95% CI	
						Lower	Upper
NPI	−2.47	167.65	0.014	−5.58	2.26	−10.04	−1.13
BPRS	−2.94	182.70	0.004	−14.1	4.82	−-23.63	−4.63

6.4.8. Psychiatric Co-morbidity as Assessed by the Present State Examination in a Cognitively Unimpaired Subgroup

Sixty-four subjects judged to be suitable for a full psychiatric interview were examined by this researcher using the PSE components of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (WHO, 1990) and an ICD-10 diagnosis made where relevant. 13 of 66 subjects (19.7%) thus examined met ICD-10 criteria for a psychiatric diagnosis. The ICD-10 psychiatric diagnosis thus made, are enumerated in Table 31.

Table 31. ICD-10 psychiatric diagnoses in institutionalised subjects with epilepsy.

ICD category	Frequency (64 cases)	Percent(%)
Organic mental disorders	0	0
Alcohol/substance abuse	0	0
Psychoses	0	0
Alcohol/substance abuse	0	0
Depression	11	16.7
Anxiety/neurotic disorders	1	1.5
Somatoform/dissociative disorders	1	1.5
Eating/sleep/sexual disorders	2	3.0

We also estimated clinically significant symptoms as rated by the clinician, using the Present State Examination components of the Schedules for Clinical Assessment in Neuropsychiatry (WHO, 1992b). A symptom category was rated positive if the subject in question was found to have three or more clinically significant symptoms in that category, clinically significance indicating that the symptoms were not just present, but disabling. Of sixty-four subjects who had clinical symptom ratings performed in this way, 31 (48.4%) rated positive on at least one PSE symptom category. The prevalence of clinically significant PSE symptoms is detailed in Table 32.

Table 32. Clinically significant PSE symptoms in institutionalised patients with epilepsy.

PSE symptom category	Frequency (64 cases)	%
Somatoform	4	6.3
Worrying/tension	14	21.9
Panic/anxiety	15	23.8
Obsessional	5	7.8
Depressive	9	14.1
Decreased concentration/thinking/energy/interests	5	7.8
Sleep/appetite	10	15.6
Eating disorder	4	6.3
Expansive mood	2	3.1
Alcohol/substance abuse	2	3.1
Psychotic symptoms	6	9.4

We examined agreement between ICD-10 diagnosis and clinically significant PSE symptoms as valid measures of psychiatric caseness in this population. A Kappa of 0.31 was estimated (CI: 1.7–43.6)

6.4.9. Epilepsy Specific Psychopathology as Assessed by the Neurobehavioral Inventory (NBI)

Subjects who were cognitively unimpaired, and their professional carers, were asked to complete the patient and carer versions respectively of the NBI. Sixty respondents completed both patient and carer versions of the NBI inventory.

We examined spearman correlations between patient and carer measures of the NBI. Correlations were modest, and only in a few subscales did they reach statistical significance, notably, religion (Rho=0.35, p=0.006); temper (Rho=0.31, p=0.015); sex (Rho=0.28, p=0.030); fear (Rho=0.29, p=0.023); seriousness (Rho=0.48, p<0.001); emotionality (Rho= 0.42, p= 0.001); persistence (Rho=0.37, p=0.004) and hatred (Rho=0.30, p=0.021).

A positive rating in an individual symptom category was made with a score of 2 or more (5 being maximum) in that category, in line with recommendations made by Blumer (1995). Table 33 depicts the frequency of patient and carer reported symptoms on the NBI.

Table 33. NBI patient and carer-rated symptomatology.

NBI Scale	Frequency (patient)	%	Frequency (carer)	%
Writing	3	5.0	2	3.3
Morals	12	20.0	2	3.3
Religion	18	30.0	3	5.0
Temper	7	11.7	9	15.0
Order	9	15.0	2	3.3
Sex	13	21.7	5	8.3
Fear	5	8.3	1	1.7
Guilt	5	8.3	1	1.7
Seriousness	12	20.0	1	1.7
Sadness	5	8.3	3	5.0
Emotionality	14	23.3	8	13.3
Suspiciousness	5	8.3	0	0.0
Detail	20	33.3	8	13.3
Cosmic interests	15	25.0	1	1.7
Destiny	13	21.7	3	5.0
Persistence	5	8.3	11	18.3
Hatred	2	3.3	5	8.3
Dependence	6	10.0	2	3.3
Happiness	5	8.3	2	3.3
Physical	8	13.3	1	1.7

6.4.10. Comparison of Psychiatric Measures Against One Another and with the Gold Standards of "Clinical Significance" and "ICD-10 Diagnosis"

We compared the NPI, BPRS, and NBI patient and carer scales with one another and as measures of psychiatric caseness against the two gold-standards for psychiatric diagnosis; the rating of "clinical significance" based on the PSE interview (described above) and ICD-10 diagnosis derived using the SCAN program. Receiver Operating Characteristics (ROC) Analysis was used to perform these comparisons.

None of the instruments appeared to perform well against either gold standard-clinical significance or ICD diagnosis. The ROC curves for clinical significance (Fig. 19) and ICD-10 diagnosis (Fig. 20) are depicted below with tables 34 & 35 detailing the area under the curve in each case.

Figure 19. ROC curve depicting performance of the NPI, BPRS and NBI (patient and carer scales) against the "clinical significance" gold standard.

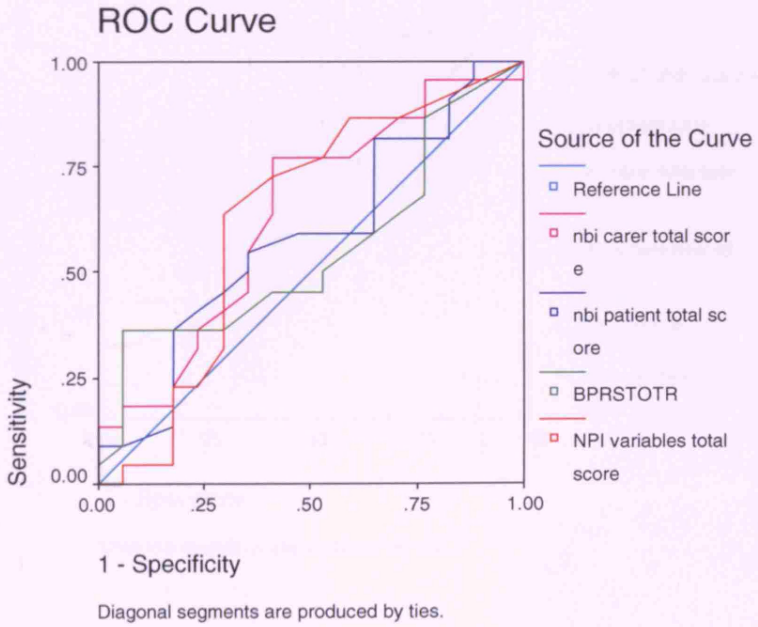


Table 34. Area under the curve- clinical significance gold standard.

	Area	Std. Error	Asymptotic 95% Confidence Interval	
Test Result Variable(s)			Lower Bound	Upper Bound
NPI variables total score	6.3	0.1	0.44	0.82
BPRSTOTL	0.55	0.09	0.37	0.73
NBI patient total score	0.58	0.09	0.40	0.77
NBI carer total score	0.64	0.09	0.46	0.82

Figure 20. ROC curve depicting performance of the NPI, BPRS and NBI (patient and carer scales) against the "ICD-10" gold standard.

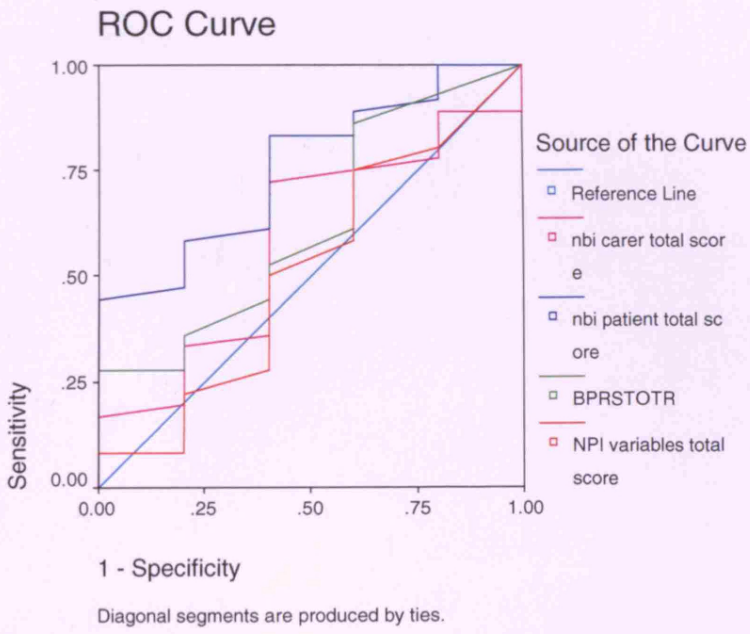


Table 35. Area under the curve: ICD-10 gold standard.

	Area	Std. Error		Asymptotic 95% confidence Interval	
Test result variable(s)			Asymptotic Sig.	Lower bound	Upper bound
NPI variables total score	0.51	0.15	0.22	0.80	0.51
BPRSTOTL	0.62	0.13	0.35	0.88	0.62
NBI patient total score	0.76	0.10	0.56	0.96	0.76
NBI carer total score	0.58	0.13	0.32	0.85	0.58

Table 36 depicts the cut off score for each instrument that yields the best match of sensitivity and specificity. As is evident, the sensitivity and specificity of these measures as global measures of psychiatric caseness is generally poor, with the cut-off scores being rather low.

Table 36. Sensitivity and specificity of the NPI, BPRS, NBI-P and NBI-C against the ICD-10 and clinical significance gold-standard.

Instrument	Cut-off score (ICD)	Sensitivity (%)	Specificity (%)	Cut-off score (CS)	Sensitivity (%)	Specificity (%)
NPI	1/2	60	75	1/2	58.8	86.4
	2/3	60	66.7	2/3	52.9	77.3
	3/4	60	58.3	3/4	41.2	72.7
BPRS	3/4	60	77.8	3/4	76.5	77.3
	4/5	60	72.2	4/5	70.6	72.7
	5/6	60	66.5	5/6	64.7	68.2
NBI-P	14/15	80	91.7	14/15	88.2	95.5
	15/16	60	88.9	15/16	82.4	90.9
	16/17	60	86.1			
				18/19	82.4	86.4
				21/22	82.4	81.8
NBI-C	8/9	80	86.1			
	9/10	80	83.3	9/10	76.4	86.4
	10/11	80	77.8	10/11	70.6	86.4
				11/12	58.8	77.3

7. DISCUSSION OF THE RESULTS: PRIMARY CARE STUDY

7.1. Critique of Primary Care Study

7.1.1. Factors Inherent to this Study

While the results reported herein are in line with prediction, a number of factors could have influenced these findings. These are considered in detail herein.

7.1.1.1.Response Rates:

The response rate in the primary care study was low in both settings King's Lynn and Bradford. Only 43% of 193 subjects with epilepsy who were invited to take part in the study eventually took part. A significant proportion (over half) either refused (26%) or failed to respond to the invitation (31%). The response rate in control subjects was similarly low. Of 582 controls contacted, 51.3% failed to respond to three letters of invitation, and 22.4% dropped out having accepted. This of course may influence the results as it may have caused a "response bias", with subjects who agreed to take part in the study, being non-representative of the population as a whole, either because they suffered from a greater burden of psychosocial morbidity (hence the interest in participation) or because they did not recognise these complaints (hence the lack of interest in taking part).

It would have been ideal to compare responders and non-responders and study these characteristics based on available information in the GP records. However, this was not possible, as the study was not adequately resourced for such an extensive exploratory investigation. Personal or telephonic contact with suitable subjects may also

have increased the response rate. This too could not be undertaken both for resource and ethical reasons. We did however encourage participation via the public communications and the specialist epilepsy nurse service. Other perceptible reasons for the low response rates that were put forward locally in King's Lynn and Bradford included

a. Recent epilepsy research efforts in the locality (King's Lynn) (O'Donoghue et al, 1999)
b. A general mistrust of such efforts and poor response rates as a whole (Bradford)
c. The subject of study, psychological burden, which may not have appealed to many potential participants.

Psychological morbidity rates were low in both persons with epilepsy (about 19%) and control subjects (about 8%) in comparison to published results elsewhere (over 40% and 15% respectively) (Edeh & Toone, 1988; Jenkins et al, 1998). The response bias therefore is likely to have been skewed in the negative direction, in both groups. It may be argued that the difference in psychiatric co-morbidity between the two groups therefore, was demonstrated despite this low level of co-morbidity, rather than because of it, as the reductions in comparison to published figures, are approximately equal in both epilepsy and control groups. However, in the light of the generally low response rates, and the considerable consequent potential for bias, we must be guarded in the inferences drawn regarding the observed differences.

7.1.1.2.Choice of Study Locations

It is widely acknowledged within the UK, that neither King's Lynn nor Bradford can be described precisely as representative of the UK population as a whole. An interesting demographic contrast for example is that King's Lynn has among the lowest proportions of non-white residents much below the national average, while Bradford has among the highest, much above the national average. Both locations fall below the national average in terms of opportunity, performance and social indicators. We chose the locations for a range of pragmatic reasons, the presence in both locations of a primary care service and register for epilepsy lead by a senior clinician based in primary care, key factors in conducting a study of this magnitude, with few resources. However, these factors (including a significant primary care interest in epilepsy) may also contribute to reducing the representative nature of these populations, and this too needs to be acknowledged. It is not unknown for example for people to move residence in order to be within the catchment area of a responsive clinical service.

We do acknowledge therefore that the locations we chose could have per se introduced an element of selection bias, resulting in results that may not be readily extrapolated to other UK populations or those elsewhere, but do not feel that these are in excess of normal populations variations that are commonplace in epidemiology.

7.1.1.3. Level of Ascertainment – Epilepsy and Psychiatric Caseness

Cases of epilepsy for this study were recruited from the epilepsy register maintained in the King's Lynn practice, and maintained by the Bradford Epilepsy Service. Both

registers had been established in rather similar ways, using a two-stage procedure to screen the records and identify all possible cases, followed by a personal examination of all cases by a neurologist (described in papers by O'Donoghue et al, 1999; Wright et al, 2000 respectively). This is the widely accepted method of ascertainment in epidemiology, as investigative evidence and the level of detail one has come to expect in hospital settings, do not exist in primary care.

All cases were reappraised by this candidate, an experienced clinician trained in psychiatry and neurology, and with an epilepsy interest. All patients included were determined clinically to have epilepsy, which met ILAE criteria for active epilepsy. There is a misdiagnosis rate of up to 20% in many settings including specialist settings, patients diagnosed to have epilepsy actually suffering from non-epileptic attack disorder and such like (Betts, 2002). This is a problem that afflicts all epidemiological studies of epilepsy, and one that is likely to impact on the present study, but no more than any other. There were variations in the methods used to establish these registers, the King's Lynn register being established using more rigorous case-finding methodology when compared to the Bradford register. The reasons for this difference were

a. The significantly smaller size of the King's Lynn register which covered 2 practices in the locality, unlike the Bradford register which involved an entire Primary Healthcare Group (PCG).
b. The academic purpose of the King's Lynn register, which was part of a PhD study, as opposed to the Bradford register, which was established, to meet a local health service need.

We however made efforts to ensure that only cases with active epilepsy were included, by:

a. Carrying out our own searches of computer records, updating both epilepsy registers in the process
b. Matching our searches with the established registers, and including only those subjects who met criteria for active epilepsy as defined herein
c. Excluding at the outset cases in whom diagnosis was in doubt
d. Reappraisal of diagnosis being carried out by this candidate

We included a sample of subjects from the Southgate Surgery in King's Lynn, which did not have an established register, and wished to establish such a register. In doing this we helped to fulfil a local primary care need. The procedures used for this screening were rigorous, and mirrored those used in the earlier studies. This candidate carried out the confirmation of diagnosis. In the event, only nine subjects with epilepsy from this practice eventually took part in our study, and are included in the epilepsy group. Admittedly, the inclusion of this group may have increased marginally the misdiagnosis rate in our sample, although we have no reason from our clinical examinations and review of records to believe that this is so.

7.1.1.4. Burden of Instruments

The employment of multiple measures, with potential for overlap, may have influenced the findings of our study, as this increases the likelihood of inaccurate or

invalid responses. While we did use a number of measures in this study, we did by staggering their administration in a systematic way attempt reduce the burden. Thus all subjects received the self-rating measures, GHQ-28, HADS and SHE by post at which time an appointment was also made by the investigator to see them. They were requested to attend this appointment with the completed measures in hand. During the appointment they were assessed with the MMSE, NHS3 and CIS-R in that order. Subjects taking part in the second stage PSE/SCAN interview were then given the NBI to take home and complete (both patient and carer version) to bring with them to the appointment for the lengthier PSE/SCAN interview. All these appointments were made within the span of one month (within the week in most cases), 1 month being the duration of the "present state" assessed in all measures. By adopting this systematic and staggered procedure of instrument administration we believe we managed to maintain consistency and avoid the problems of instrument burden.

7.1.2. Factors Influencing Results in Epidemiology and Their Relevance to the Primary Care Study

Inference is described as "the process of passing from observations to generalisations". A number of factors are known to influence results in psychiatric epidemiology and to thus affect inferences made from epidemiological studies. An observed association between two factors does not mean that they definitely caused one another. Thus in epidemiology, before any consideration of cause and effect may be entered into, the role of chance, bias, confounding and direction of causality needs to be considered (Stewart, 2003).

7.1.2.1. Chance

Chance operates through sampling error. We hypothesised in this study that cases with epilepsy were twice as likely as controls to suffer from co-morbid psychiatric disorder. We did indeed find such a difference in the population we studied, in the overall sample. In doing so, we believe that we have rejected the null hypothesis, i.e. that there is no difference in the prevalence of psychopathology between cases with epilepsy and controls, this inference being supported by the mean score and narrow confidence interval value. The finding could, however, still be a product of chance, as revealed by the failure to demonstrate a significant difference between cases and controls in the paired samples *t*-test.

In mitigation, the consistent trend in results, in line with prediction, the good agreement in general among the instruments of psychiatric research employed, the significant "*p*" values, and not too wide confidence intervals of the difference between patient and control means, appear to indicate that the findings of our study are not merely an artefact of chance, and represent true differences between epilepsy and control populations.

7.1.2.2.Bias

Bias refers to systematic error arising from the design or execution of a study. Unlike confounding, bias cannot be "adjusted for" once data has been gathered. Bias can be categorised into that which arises from deriving the sample or comparison groups from

the base population (selection bias) and that which arises from measurements made on study participants (information bias) (Stewart, 2003).

Information Bias:

This arises from a systematic error in the measurements applied, all measurements being potentially subject to error. Recall Bias is an important source of information bias, and could have impacted on the present study. However, as the period of examination (the present state) was one-month in all measures employed, and this is a relatively short period, the likelihood of the period per se causing recall bias is low. However, the possibility that people with epilepsy would be more likely to report changes to their mental state when compared to their peers in the community remains, given the chronic nature of epilepsy, and the considerable stigma attached to the illness. Further, people with epilepsy may be more forthcoming about mental symptoms than their peers in the population, considering these to be part of the illness, rather than an aberration in mood or behavior. These sources of recall bias albeit negligible, need consideration. Another form of information bias that may have influenced the results in this study is observer bias. The observers in phase-1 and phase-2 were not blinded to the disease status (group) of the individual participant being studied. However, the instruments employed in phase-1 such as HADS, GHQ-28, and CIS-R were largely structured and self-rating thus restricting the potential for observer bias. In phase-2 the interviewer while being aware that all participants had epilepsy, was blinded to the results of their phase-1 evaluation, both epilepsy and mental disorder variables. Thus there was an inherent source of observer bias, with the likelihood that common mental disorder symptoms may be over-rated by this observer on PSE-SCAN interview, given the knowledge that the participants in phase-2 had epilepsy, and the belief that persons

with epilepsy had higher rates of psychiatric disorder. However, the good agreement demonstrated between the structured instruments employed in phase-1 and the results of the PSE-SCAN interview, it may be argued that the impact of such bias, if any, on the results of this study was probably low.

The employment of multiple measures all measuring common mental disorder may have led to error. It is well known that "re-testing" often results in conflicting or inaccurate responses in clinical research settings. The measures were employed in a systematic manner in all cases, the period of measurement (present state) was adhered to and was consistent across measures, and the results across measures were consistent as indicated by their general agreement. Random error would have led to underestimation of the association under study.

Selection Bias:

A further form of bias that affects case-control studies in particular is selection bias. This arises from the failure of cases or controls being recruited to the study in question to be representative of cases and controls in the population as a whole. Selection bias may occur when the classification as case or control is to some extent dependent upon an exposure under study as a hypothesized risk factor. That both the base population from which cases and controls were drawn for this study may be unrepresentative of the UK has been acknowledged herein. Further, as pointed out earlier, factors such as the low response rates, the existence of a primary care based service for epilepsy, may all have resulted in a degree of selection bias creeping into this study.

In this case there is also a theoretical possibility that the exposure under study, common mental disorder, may by itself influence the selection of cases or controls. It is well known that seizures are over-represented in depression (ref- Hauser) as depression is in epilepsy. A number of factors may be responsible for this: shared biological risk/mechanisms, the use of psychotropic drugs (which are proconvulsant) in the treatment of common mental disorder, lifestyle and socio-cultural issues etc., which will be addressed further in the "direction of causality" section. It is not clear whether in this study this factor may have influenced the choice of case or controls. We took care to include as cases only those subjects with active epilepsy as defined by ILAE. We also employed fairly rigid exclusion criteria, ensuring thus that patients with active epilepsy alone were included. Nevertheless, our criteria do not specifically exclude patients judged to have symptomatic seizures, this being difficult to establish in a community study. It is possible therefore that these factors may have induced a degree of selection bias.

Prevalence Bias:

Prevalence (proportion of people with the illness at any a particular period of time) is a product of both incidence (number of new cases with the illness during the time period) and number of cases who cease to have the condition during the period, due to recovery or death. In general, epilepsy is a condition with significant morbidity and mortality (Sander, 2002) and this creates the potential for prevalence bias. Exposures associated with epilepsy may in fact be associated with survival with epilepsy rather than with incidence of epilepsy per se. This is a theoretical (although, arguably, unlikely) possibility with respect to common mental disorder, since prevalent as well as more recently incident cases were included.

7.1.2.3. Confounding

Confounding describes a situation in which the measured effect of an exposure is distorted by the association of that exposure with other factors that influence the disease or outcome under study. Confounding may result in true associations being missed as well as false associations being identified (Stewart, 2003). A number of factors that may confound the results of this case control study were eliminated through the employment of rigid exclusion criteria. These included age (paediatric and geriatric populations having different causes, rates and manifestations of epilepsy being excluded); learning disability (both epilepsy and mental disorder are over-represented in learning disabled populations); serious co-morbid physical illness and/or disability (which may independently be associated with CMD); and non-English speaking populations who may have other causes, rates and manifestations of epilepsy and/or CMD. The role of Anti-Epileptic drugs (AEDs) in the development of psychopathology must also be considered as reviewed earlier. Further, the role of ongoing sub-clinical seizure activity in the development of psychopathology must be kept in mind.

We have not controlled for AEDs in the cases as in a population study this would have been difficult to achieve, and because systematic approaches to this (scales for example) are lacking. There was also the issue of instrument burden and resource limitation. We have not controlled for seizure activity manifesting as psychopathology, as this would have involved doing EEG's in all persons with epilepsy, which is beyond the scope of this investigation, and for which the resources

were not available. Both these factors may have influenced the burden of psychopathology in the cases (not in controls), and may in part account for the increased burden of psychiatric co-morbidity in cases with epilepsy in this population.

Other potential confounders that have not been accounted for in this study include life events and social class, factors that are known to impact on mental state in both patients with epilepsy and control populations. We did not include a life events scale in this study, partly in order not to increase instrument burden, and partly because such a scale would have to be adapted for use in epilepsy. For example, "temporality of seizures" is known to be an important factor that mediates mood in people with epilepsy. Life-event scales employed in epilepsy need to incorporate questions about seizures as life events and their putative impact on (present) mental state. We also did not measure social class in any systematic manner, mainly due to the poor resourcing of the study. Social class may be associated with both CMD and epilepsy. Other important variables such as social support, education and employment status are also potential confounders that we have failed to take account of in a systematic manner.

It must be therefore be acknowledged that these potential sources of confounding may influence the results reported herein. Collecting baseline data on these potential confounders may have been beneficial, as it would have enabled us to adjust for these factors in the analysis.

However, the in-depth statistical analysis described previously using multivariate methods, has enabled taking into account some potential confounders. The use of Generalised Linear Modelling (GLM) SPSS in order to study the complex

relationships between seizures, CMD and disablement has helped to establish beyond reasonable doubt that an association between CMD and disablement exists, and that it is independent of the association between seizures and disablement.

7.1.2.4. Direction of Causality

Could there be a cause-effect relationship in the reverse direction to the one anticipated? Such "reverse causality" is possible in studies of this nature. For example in this study the presumed direction of causality is that of epilepsy causing CMD, more often when compared to control populations without epilepsy. In other words epilepsy is assumed to be the risk factor that provokes CMD. An alternate possibility of course is that the cause-effect relationship operates in the reverse direction, with CMD causing epilepsy in some subjects but not others, within the population surveyed. In general, CMD is a more common (about 20% of populations surveyed) when compared to epilepsy (5 per thousand in most population studies). Further, there is epidemiological evidence to suggest that depression for example is a risk factor for the development of seizures, for reasons discussed earlier in this chapter. A causal relationship in the reverse direction is therefore possible. However, the consensus in epilepsy research, with epilepsy being a significant neurological illness, with a biological basis in the limbic system in most cases, and with significant morbidity, mortality and disablement, tends to veer towards epilepsy being a cause of depression and other psychiatric disorders (Kanner, 2003). Whatever the direction of causality however, the effort in this study is to demonstrate a greater burden of CMD in epilepsy as compared to that seen in a matched control population, which we have demonstrated.

7.1.3. Discussion of the Results

7.1.3.1. Hypothesis- Common Mental Disorders ARE Commoner in Epilepsy

Our findings are in line with prediction. Common mental disorders are commoner in patients with epilepsy when compared to population based controls, the difference being statistically significant. Patients with epilepsy were significantly more likely to have a primary psychiatric diagnosis (ICD-10) derived from the CIS-R interview. Although there has been considerable evidence to suggest the over-representation of psychiatric disorders in patients with epilepsy, this is to our best knowledge the first primary care based, hypothesis driven study that has used valid instruments of psychiatric research, and matched population based controls to confirm this increased burden of psychological morbidity. The demonstration of significantly higher co-morbidity of CMD in the epilepsy group, both in the overall samples, and in the paired samples design, is evidence that CMD are over-represented in epilepsy.

There were interesting differences too in the patterns of psychiatric co-morbidity in epilepsy. Mild depressive episode and mixed anxiety and depression were the two diagnoses identified both in controls, and in patients with epilepsy. Patients with epilepsy however demonstrated a wide spread of other ICD-10 psychiatric diagnoses including moderate depressive episode, severe depressive episode, specific (isolated) phobia, obsessive-compulsive disorder, and social phobia. Patients with epilepsy were also more likely than control subjects to have a secondary psychiatric diagnosis (ICD-10). Indeed no control subject (111) met ICD-10 criteria for a secondary psychiatric diagnosis in comparison to six of 59 subjects with epilepsy.

There were interesting differences too both in the burden of psychological morbidity and in the patterns of psychological symptoms expressed between the two groups. Patients with epilepsy were more likely to suffer from poor concentration, depression, worry, worry over physical health and compulsions, when compared to their peers in the population. The "load" of psychological symptoms was also greater in the epilepsy group; mean CIS-R total scores being significantly more in this group when compared to controls.

Overall, these results indicate an increased burden of psychiatric co-morbidity in epilepsy, in terms of symptom severity and multiplicity (load). While these factors may result in patients with epilepsy meeting criteria for a diagnosable psychiatric disorder, this is by no means assured, as criteria based instruments differ considerably from symptom-based measures. Given these findings, we may argue that symptom based measures are more likely to reflect the true burden of psychological morbidity in epilepsy, and that the use of such measures is a more valid and reliable technique in epilepsy research. Further, these findings are in keeping with past evidence reviewed herein as well as empirical observation. The fact that they arise from a relatively representative population in primary care, increase their validity, and provide the necessary evidence to inform and influence public health planners and providers about the importance of psychiatric issues in epilepsy.

7.1.3.2. Agreement between Screening and Diagnostic Measures in Patient and Control Groups

Unlike the diagnostic measure used in the case-control component of the study, the CIS-R, which showed a difference in total scores between patients and controls, the screening measures, HADS and GHQ-28 (with the exception of the somatic symptom scale on GHQ-28) failed to show differences between the two groups in terms of mean total scores. As the HADS has been used in a number of population studies in epilepsy, as a measure of psychiatric caseness, we used the cut off score of 11 to diagnose anxiety and depression based on the respective subscales, and found no difference between patient and control groups in terms of psychiatric caseness. When non-parametric correlations were examined, the two screening measures appeared to agree with one another and with the CIS-R in both groups, although the correlation co-efficient values were higher in the control group than the epilepsy group (tables 5 & 6).

The results of the ROC analysis show that the screening measures GHQ-28 and HADS perform reasonably well against the CIS-R gold standard of psychiatric caseness, in both epilepsy and control groups, with sensitivity and specificity of generally above 80%. However, it is interesting to note that,

a. The cut-off scores that indicate psychiatric caseness are considerably lower in both epilepsy and control populations than employed in previously published studies of HADS (Baker et al, 1996; Jacoby et al, 1996; O'Donoghue et al, 1999 for example)

b. The cut off scores that corresponded with psychiatric caseness on the CIS-R were lower in controls than in persons with epilepsy for both the GHQ-28 and HADS-Anxiety subscales, and comparable for the depression subscale.

These results indicate that while it would be acceptable to utilise these screening measures in large population based studies, thus making these studies more economical, less time consuming, and viable, the cut off scores for "caseness" may need to be suitably revised in order to identify all subjects with psychological morbidity. Indeed, it is entirely possible that the estimates of psychological morbidity published in previous studies, using these screening measures with previously published cut off scores derived from non-epilepsy populations, have been lower that the actual morbidity that may have existed in the communities surveyed.

There are of course other explanations for these lower cut off scores in the two groups, including:

a. The presence of a generally high level of psychological morbidity in the participants, not supported by the overall levels of psychiatric caseness which were generally low
b. A lack of consistency in responses to these measures (not supported again due to the high correlations between the measures employed).

Interestingly also, the greater consistency across measures in the control group, did not yield cut-off scores in this group that were more in line with published literature.

Needless to say, as discussed earlier, a response bias may have been operational and contributed to these results as discussed extensively earlier in this section.

7.1.3.3. Psychotic Symptoms in Patients and Controls

13.6% of patients with epilepsy as opposed to 3.6% of controls scored positively on the Psychosis Symptom Questionnaire, the difference being statistically significant. This is in line with prediction, as the vast majority of studies (for example: Bredjkaer et al, 1998: Stefansson et al, 1998) have shown an over-representation of psychosis in patients epilepsy, which has also been consistently predicted in expert reviews of the literature.

PSQ has been noted to have poor specificity in population based research (Jenkins et al, 1998), and comparison with a gold standard such as SCAN or CIDI would be necessary, before the results of this screening test can be accepted. Indeed, the comparison of the PSQ with SCAN described in the results section, highlights the importance of this. The use of the PSQ in population-based studies of epilepsy must therefore be judicious, and after taking into consideration items like question-1 "Over the past year, have there been times when you felt very happy indeed without a break for days on end?" This particular question may need alteration in our opinion, as a number of cases and controls when first asked the question were puzzled by it, and sometimes answered in the affirmative. Cross checking and repeated clarifications by the interviewer were required in many cases.

7.1.3.4. Psychiatric Disorders in Patients with Epilepsy

7.1.3.4.1.Psychiatric caseness in epilepsy: comparison of ICD, clinical significance and CIS-R

55 of 59 subjects with epilepsy completed the PSE components of the SCAN interview with this candidate. 29.1% of subjects met criteria for at least one ICD-10 diagnosis. Of the broad diagnostic categories depressive disorders followed by anxiety disorders were the most common, in line with previous research findings reviewed herein. and in line with prediction.

In contrast 40% of 55 subjects with epilepsy were rated positive on at least one PSE symptom category. The most common symptom categories were biological (sleep, appetite, weight and sexual function); worry; anxiety & panic; depression; and somatoform symptoms in that order, representing the spectrum of common mental disorder symptomatology. Indeed, when clinical significance ratings and ICD-10 categories were compared, correlations between key common mental disorder symptom categories became immediately apparent, underlining the importance of this construct in the psychiatric epidemiology of epilepsy. The higher prevalence of clinically significant symptoms when compared to ICD-10 diagnoses is in line with prediction. Taken together with the earlier finding that that lower scores on screening instruments appear to correlate with psychological morbidity, these data appear to reinforce the importance of symptom based approaches to diagnoses in epilepsy studies, as well as the potential pitfalls of relying exclusively on structured criteria based diagnostic approaches in these special populations.

It is noteworthy also that clinical significance ratings of psychiatric caseness were highly correlated with ICD-10 diagnosis. Interestingly, when CIS-R derived caseness was compared with caseness derived through clinical significance ratings on PSE, and with ICD-10 diagnosis derived through the PSE interview, there was greater agreement between the CIS-R and ICD-10 ratings of caseness, than between CIS-R and clinical significance ratings. While in part this may be explained by the CIS-R relying on ICD-10 diagnostic rules to make ratings of psychiatric caseness, it nevertheless is surprising, as greater agreement between two symptom based measures (CIS-R and clinical significance) was expected.

7.1.3.4.2. Measures of Psychiatric Caseness: A Comparative Analysis

When the screening instruments employed in this study, the GHQ-28 and HADS, and the diagnostic instrument used (CIS-R), were compared using ROC analysis with the two gold standards of psychiatric caseness, ICD-10 diagnosis and clinical significance, a number of interesting observations emerged. First, all three instruments compared well with both gold standards. Second, subtle differences in performance became apparent: the CIS-R performing best, followed by the HADS and then the GHQ in relation to both gold standards. Third, a suggestion that clinical significance ratings compared better overall with the instrument ratings, rather than ICD-10 diagnosis, as revealed by the area under the curve in the two ROC analysis (figures 12&13).

Interestingly, in this analysis also, the cut off scores of the different instruments were lower when compared with the clinical significance gold standard as

opposed to the ICD-10 gold standard. Indeed, the scales when compared with ICD-10 appeared to follow established cut-off scores for caseness for several of the instruments including CIS-R=11.5 (Lewis G et al, 1992); HADS- Anxiety= 8.5 (O'Donoghue, 1999); and GHQ-28= 20.5 (Goldberg, 1988), but not HADS-Depression which at 3.5 was much lower. In contrast the corresponding scores for the clinical significance gold standard were CIS-R= 6.5; GHQ-28= 17.5; HADS-Anxiety= 7.5; and HADS-Depression= 3.5. We may on the one hand assume based on these results that the cut off scores with ICD-10 diagnosis are the ideal, compare as they do with published cut-off scores. On the other hand, this is but to be expected, as the cut off scores are derived in studies that have used the very same criteria based gold standards. The interesting counterpoint therefore is whether the clinical significance gold standard is a better gold standard to apply in epilepsy studies, not only because it appears to perform well in the ROC analysis, but also because it is symptom based, more sensitive to psychological morbidity, and more likely to diagnose "cases" with disabling psychiatric symptoms. These results appear to indicate therefore that the established gold standards with which we compare screening and diagnostic measures may need to be reviewed.

In contrast, the psychosis symptom questionnaire did not agree with either the ICD-10 diagnosis or the clinical significance gold standards. The results once again demonstrate the high sensitivity but poor specificity of this measure (Bebbington & Nayani, 1995), even in a population with epilepsy and with theoretically, an increased prevalence of psychosis. Currently a positive rating on a single question on this measure is adequate to ensure scale positivity. The question most likely to yield a false positive response was in our observation the question relating to Hypomania

"Over the past year, have there been times when you felt very happy indeed without a break for days on end" (Appendices Section 9.3, pg. 363) and this as mentioned earlier may be subject to revision.

While the importance of such a screening measure for population based research cannot be underscored, the scale perhaps needs to be altered to provide a safety net especially for vulnerable items such as that aforementioned.

7.1.3.4.3. The Neurobehavioral Inventory (NBI): A Valid Measure of "Psychiatric Caseness"

The analysis of the NBI showed that a significant prevalence of its constituent symptoms was present, even in this community based sample. Although the patient and carer responses in the NBI exhibited good agreement, the comparisons of these measures against three different gold standards, CIS-R derived ICD-10 diagnosis, clinical significance based on the PSE interview, and SCAN derived ICD-10 diagnosis, demonstrated quite clearly, the superior ability of the patient questionnaire as a measure of psychiatric caseness. Total scores on the patient questionnaire were able to discriminate psychiatric cases from non-cases, across the three measures, agreement being best with the CIS-R, less robust with clinical significance ratings based on the PSE interview, and least robust based on ICD-10 criteria based diagnosis.

The superior ability of the patient measure as opposed to the carer measure is expected, this being a primary care sample of non-cognitively impaired subjects. The

better agreement with the CIS-R is also understandable, the CIS-R being a symptom based measure, and thus similar to the NBI. While the superior agreement between the NBI and the clinical significance ratings may also be explained by the symptom based nature of such ratings, it illustrates once again the greater sensitivity of the clinical significance gold standard, as opposed to criterion based gold standards such as ICD-10.

Even more interesting perhaps is the demonstrable ability of the NBI, a measure of epilepsy specific psychopathology, to compare well with generic measures of psychiatric caseness. There are several possibilities in this regard. First, the NBI, although it is intended to be a measure of epilepsy specific psychopathology, may actually be measuring generic psychopathology. Second, both generic and epilepsy specific psychopathology may co-exist in a number of patients with epilepsy and the association demonstrated may be a chance association. Third, the burden of epilepsy specific psychopathology may influence generic psychopathology scores adequately, in order for patients to score positively on these measures. Fourth, the concept of epilepsy specific psychopathology may be erroneous, the behaviours observed being no more than indicators of generic psychopathology: stickiness a reflection of obsessionality, suspiciousness a reflection of paranoid ideation, and so on, as many dissenting reviewers have often commented (Devinsky, 1999). Finally, a degree of epilepsy specific psychopathology may be present in all individuals with demonstrable temporal lobe pathology (such as hippocampal sclerosis), these cases constituting between 30 and 40% of a community-based sample such as this. What is described as epilepsy specific psychopathology may therefore be no more than end of spectrum "normal" behaviours seen in people with brain disease. The implications of

these findings for epidemiological research, and employment of the NBI in future studies are discussed section 7.1.3.4.3 (pg. 283) below.

7.1.4. Seizure Severity, Psychiatric Co-morbidity & Subjective Handicap

Seizure severity was measured using the National Hospital Seizure Severity Scale (NHS3) a validated measure, and was not associated with either generic or epilepsy specific psychopathology in our study. This is not in line with prediction, a number of previous studies have demonstrated clear associations between the severity of seizures and co-morbid psychopathology (Jacoby, 1996; Baker, 1996). That having been said, the assessment of psychiatric co-morbidity in a number of these studies has left much to be desired, hitherto un-validated screening measures such as HADS being employed to discriminate psychiatric cases from non-cases in many studies.

Other seizure related measures that have been associated with psychological morbidity include seizure frequency, which we did not measure in our study as we found this to be subjective, unreliable, and a validated instrument for measurement of the same lacking. Other variables that have been associated with psychosocial outcome include temporality of last seizure, type of seizure, and the prescription of AEDs (Baker et al, 1996). We did not classify the type of seizure, as such a classification would have been based on clinical impressions, and made in the absence of supportive investigations, this being a community based study. In hindsight, however, the recording of this information may have provided interesting insights.

Seizure severity was however associated strongly with many scales on the disablement measure, in line with prediction. Having more than one type of seizure was as expected more disabling. Further, total seizure severity scores were associated with all scales on the disablement measure except the work scale, indicating that increased seizure severity impacted on several aspects of the patients life including physical, social, self-perception and life-satisfaction. The impact of seizure severity on psychosocial variables has been well demonstrated in a number of studies and in a number of settings (O'Donoghue et al, 1999; Jacoby et al, 1996; Fisher et all, 2000).

Psychiatric co-morbidity was also associated with disablement, both criterion based psychiatric caseness (ICD-10 diagnosis) and psychiatric caseness evolving from symptom based measures (CIS-R), an association that has been well demonstrated in a number of studies (see Baker et al, 1996 for example).

The relative contributions of seizure severity and psychiatric co-morbidity to disablement have not been examined extensively in previous studies. Jacoby et al, 1996 showed in multivariate analysis that both psychological morbidity and seizure severity contributed to disablement in epilepsy, as did other expected predictors such as age of onset. A further report arising from this study in a large epilepsy cohort (Baker et al, 1996) did examine this issue using multivariate techniques and found psychological morbidity to explain the greatest proportion of shared variance followed by seizure severity, and other indicators. However, these studies were pedestrian in their approach to the measure of psychological morbidity, employing the HADS with published cut-off scores used in non-epilepsy populations. Our approach was to study these associations across a range of validated measures including CIS-R

derived ICD-10 diagnosis, PSE derived ratings of clinical significance, SCAN derived ICD-10 diagnosis, and NBI derived measures of psychiatric caseness.

Interestingly, it was established across the entire range of measures except the NBI carer scale, that co-morbid psychiatric disorder explained the greatest proportion of shared variance, followed by seizure severity, other predictors such as age and sex having limited effects if at all. The failure of the NBI carer scale to demonstrate such an association is not surprising, given its poor correlation to gold standards, and low levels of consistency. Indeed, this only goes to reinforce the previously stated belief herein, that such a carer rated measure may have poorer validity in adult non-cognitively impaired subjects in primary care. Of the measures employed, CIS-R appeared to be the best predictor for disablement, followed by ICD-10, and clinical significance ratings. While one might surmise that symptom load may influence disablement, and be responsible for this association between symptom based measures and disablement scales, if one were to believe that disablement scales measure what they are meant to measure, and are accurate in doing so, then surely the employment of measures of psychiatric caseness that are closely linked to such measures of disablement, is both necessary and ideal.

7.2. The Institutional Study

7.2.1. Critique of the Institutional Study

7.2.1.1. Chance

The possibility that the observations in this population are a product of chance must be considered. The patterns of psychopathology as described by NPI and BPRS in this study, are generally in line with prediction; the behaviors reported being generally observed in institutional and/or learning disabled populations. The confidence intervals of the mean score, especially with respect to the NPI scores, less so for the BPRS scores, also appear to indicate that the findings with this instrument may reflect valid associations beyond chance. Especially in the case of the NPI, NPI and BPRS correlations, both total score as well as individual items, are generally weak, and may be explained by chance. While the prevalence figures for NBI domains and PSE clinical significance ratings appear to be in line with prediction, in this population, the prevalence of various ICD-10 criteria based diagnostic categories do not, and may reflect chance outcomes, or indeed alternately reflect the relative ineffectiveness of such criteria based diagnosis in institutional populations.

When we compared NPI and BPRS scores in cognitively unimpaired and cognitively impaired populations, we found significant differences. Here too the confidence intervals for the difference in mean scores of the NPI appeared to more confidently exclude the null hypothesis value, than the confidence intervals for the mean difference in BPRS scores. It could be argued therefore that the differences observed between the cognitively unimpaired and cognitively impaired sub-groups

were less likely to be a product of chance with regards to the NPI, while chance may explain the differences observed on the BPRS.

7.2.1.2. Bias

This data emerges from a population of institutionalised individuals with epilepsy. While persons with epilepsy resident in institutions are not representative of persons with epilepsy residing in the community, they are representative of institutionalised populations as a whole, and to a lesser extent perhaps of populations with learning disability and epilepsy. Further, as pointed out in the introductory sections of the institutional study, people with epilepsy living in institutions, the main reason for their residence being epilepsy and not co-morbid learning disability or behavioural disorder, are relatively unique today. The population we have chosen is therefore in our view more representative of institutional populations with epilepsy, than those residing in mental hospitals, institutions for learning disability, and other similar locations.

The response rate in this study was in excess of 85%, considered reasonable by any standards, and it may be argued that a selection bias overall is unlikely. However, a selection bias may have been operational in the PSE-SCAN interview component of the study, as a relatively small proportion of the overall population surveyed took part in this component, and generally low levels of psychopathology meeting ICD-10 criteria were reported. We may have therefore inadvertently "selected" for this component, relatively well preserved cognitively unimpaired individuals, with low burdens of psychopathology.

A recall bias is possible, the period of the NPI ascertainment being 1 year, this being a relatively long period, and thus subject to error. From the perspective of the caregiver response, both errors of omission (driven by relatively good recent behaviour as opposed to poor past behaviour) and commission (relatively poor recent behaviour as opposed to good past behaviour) are possible. However, the overall consistency of the NPI results, which are in line with prediction mitigates against a significant recall bias having impacted on these findings. Further, factors such as seizure frequency, seizure severity, co-morbid medical illness and other outcome measures may have influenced the reporting of behaviours by the caregiver, while responding to the NPI interview.

An observer bias may have been operational in the BPRS components of the study, the ratings having been made following a thirty-minute interview and period of observation, albeit by an experienced mental health professional. This may in part explain the inconsistencies in the BPRS findings. The possibility that these inconsistencies were a product of random error as opposed to observer bias must also be kept in mind.

7.2.1.3. Confounding

Admittedly, our data have failed to take into account several potential confounding factors in studying associations between cognitive impairment and psychopathology, as the also the prevalence of psychopathology variables across instruments.

1. The role of seizure frequency and severity (difficult to operationalise in those with cognitive impairment), but with potential to impact on the results of the psychopathology outcome measures.
2. The role of anti-epileptic drugs (AEDs), difficult to operationalise as most residents were on AED polytherapy, and had been on these drugs for months if not years. However, a considerable burden of AED induced psychopathology has been reported in epilepsy, and this may be a potential confounder of psychopathology studies in populations with epilepsy. In the absence of reliable baseline data on seizure variables and AED variables, we could not adjust for these potential confounders in the analysis comparing psychopathology across cognitively impaired and unimpaired groups, and this may have impacted on the results of our study described herein.
3. The role of learning disability (neuropsychological data was not available in all residents surveyed, and the data that was available had been collected at different times using varying techniques, many residents having lived in the centre for years). However, we did study associations between cognitive impairment and psychopathology, and found the burden of psychopathology to be significantly greater in the cognitively group as opposed to the unimpaired group. While this finding was in line with prediction and present with both NPI and BPRS, the NPI findings were by virtue of their consistency and narrower confidence intervals, robust.

7.2.1.4. Direction of Causality

As in the primary care study, the direction of causality in the institutional study may have been in the direction opposite to that expected. Thus, cognitive impairment could be the result of co-morbid psychopathology rather than cause of co-morbid psychopathology. Psychopathology is well known to affect performance on cognitive tests in general, and patients with severe psychopathology, especially negative symptoms, are known to perform poorly on cognitive measures. In epilepsy, a significant association between mood change and cognition has been reported, with depression being associated with memory complaints as opposed to objective cognitive impairment (Piazzini, 2001). Further, there are reports of negative symptoms in epilepsy being associated with cognitive impairment (Getz, 2002). We did not in this study differentiate between subjective and objective cognitive impairment; nor did we distinguish between developmental and acquired cognitive impairment. Thus while we did demonstrate an association as predicted between cognitive impairment and psychopathology, and expect cognitive impairment to be the risk factor for psychopathology, we have no means of confirming that this direction of causality was operational.

7.2.2. Discussion of the Results

7.2.2.1. Documented Psychopathology in the Case Records

About a quarter of the population surveyed had previously documented psychopathology. Not surprisingly more serious forms of psychopathology, psychosis

for example, were recorded in the notes, in proportions that were in line with the published literature in epilepsy (psychosis in 7–10% of cases; Trimble, 1991), whereas the prevalence of mood disorders, depression in particular, and other common mental disorders, was lower than that expected. These results reiterate the importance of surveying institutional populations such as these, rather than relying purely on records, as only more serious forms of psychopathology tend to be documented in case records.

7.2.2.2. Descriptive Data from the NPI

Although the range of scores on the NPI was wide (0–108), the mean &median scores were generally low, the histogram being skewed to the left in line with prediction. This indicates that the vast majority of individuals scored low on this instrument, a greater burden of psychopathology (and hence higher scores) being a feature only in a proportion of this institutional population.

7.2.2.3. Factor Analysis of The NPI: A New Carer Rated Measure for Institutional Populations with Epilepsy, and Those with Learning Disability

The factor analysis of the NPI in a large number of subjects with epilepsy has yielded results that appear to be both reliable and interpretable. Four clear patterns of behaviour (factors) emerge in our interpretation of this factor analysis.

The psychosis factor, which accounts for 28.4% of the variance is characterised by delusions, hallucinations, aberrant motor behaviour and sleep

behaviour. It is well known that psychoses are over-represented in epilepsy, being several times more common in that condition, as compared to population figures (Trimble, 1991; Krishnamoorthy, 2001) and are characterised often by acute clinical manifestations of psychotic behaviour. Further, the epileptic psychoses often manifest with florid symptoms in subjects with learning disability and in those living in institutions, and the high loading on this factor may reflect the nature of the population studied. We therefore consider this factor to be clinically relevant.

We interpreted Factor-2, characterised by agitation, apathy, disinhibition and irritability as the inter-ictal dysphoric disorder (IDD) factor. IDD is a Kraeplinian concept that has been recently re-invoked in epilepsy by Blumer(1999). It is proposed, based on literature reviews and prospective investigations, that a pattern of intermittent clustering of symptoms such as depressive moods, anxiety, agitation, irritability, euphoria, inertia, insomnia, atypical pains and phobic fears (3 of 8 symptoms) over periods of two or three days is characteristic of this disorder. Factor 2 with several of the core behavioural components of that condition seems to represent IDD, accounting for 11.8% of the total variance in this group of subjects. This seems to be a reasonable assumption given that IDD may well form a substantial component of the burden of depression in epilepsy.

Factor 3, with depression and appetite change (also sleep disorder although the loading for this on the psychosis factor was higher) was interpreted as the depression factor. Co-morbid depression is common in epilepsy and is seen in over 50% of subjects in some studies (Lambert & Robertson, 1999). Further, depression of this nature is often indistinguishable from depression seen in the community and in other

chronic medical conditions (Krishnamoorthy, 2000a). We therefore interpreted this factor to represent depression of the co-morbid type. Together this factor accounting for 10.1% of the variance and the IDD factor accounting for 11.8% of the variance comprise a significant component of the shared variance, which is in keeping with the significant overall burden of depression in epilepsy.

The fourth factor characterised by anxiety and euphoria accounted for 8.5% of the total scale variance and was interpreted by us to be the anxiety factor. Anxiety is a common symptom in epilepsy (Torta & Keller, 1999) and is manifest in a number of ways including ictal anxiety, acute attacks (panic) and phobic fears. Both anxiety and euphoria are frequently observed in the period immediately following temporal lobectomy (Anhoury et al, 2000) and may well represent limbic dysfunction. Further, there is epidemiological evidence to suggest that there is a significant co-morbidity between anxiety and bipolar disorder (Angst, 1998), and the correlation between euphoria and anxiety seen here may reflect this. The presence of an anxiety factor was therefore considered to be in keeping the general patterns of co-morbid psychopathology encountered in clinical practice.

This study shows that the NPI has good internal consistency (Cronbach's α = 0.758) and its factor analysis yields a four-factor solution accounting for a good proportion of the shared variance. The factors thus derived from the NPI appear to be clinically relevant and interpretable, indicating that the NPI has face validity in this population with epilepsy. However, these results are subject to interpretation and must be treated with a degree of caution. Further studies that prospectively examine the NPI against other gold standard measures (including carer rated measures) are

required before the instrument can be adopted for widespread application. It is clear though with the limited evidence presented herein, that the NPI may well be a useful and valid carer-rated measure for the assessment of behaviour in epilepsy.

7.2.2.4. Descriptive Data from the BPRS

Like the NPI scores the BPRS scores were also generally skewed to the left, and indicated that the vast majority of subjects were rated low overall on various behavioural domains. However the range of BPRS scores was greater, and the standard deviation wider, indicating the presence of outliers. Taken together with the lower completion rates with this instrument, these data indicate that the BPRS as applied in this study has limited validity for application in epilepsy populations. This is not entirely surprising given that the BPRS was developed as an observer rated measure for use in patients with Schizophrenia and other psychotic disorders with positive and negative symptoms. The recent reports of negative symptoms in epilepsy and their relationship with cognitive status (Getz, 2002) do however provide an interesting counterpoint, and indicate the need for behavioural scales of this nature in epilepsy studies.

7.2.2.5. Agreement between NPI and BPRS

Overall agreement between NPI and BPRS total scores while present was not particularly impressive, and may be explained by chance alone. Indeed, when individual domains of NPI (12 domains) and BPRS (18 domains) were correlated, while a number of correlations in the 0.2 level emerged, they were not particularly

meaningful, nor representative of published literature as a whole. Perhaps of relevance, the key behavioural domains in the NPI, that we have come to recognize as being important in epilepsy populations: agitation, irritability, apathy, aberrant motor and sleep behaviours, correlated with more BPRS items in general, when compared with other domains of the NPI. This perhaps represents the importance of specific behaviours in epilepsy, and their tendency to influence overall psychopathology ratings. Aside from this, no meaningful interpretations could be made of NPI and BPRS correlations.

This discrepancy between caregiver (NPI) and expert-observer (BPRS) ratings may also be explained by a number of factors.

a. Difference in experience and perception of the RA, a mental health professional, and the professional caregivers (nurses and social workers) resulting in differences in the description and assessment of behavioural abnormalities.
b. The stressful nature of the assessment for the subjects- many of whom had lived in such institutional settings for years, producing unusual manifestations of their psychopathology, especially during the expert-observer interview that resulted in the BPRS ratings.
c. Erroneous ratings of psychopathology either by the expert-observer and /or the professional caregiver.

While correlations between individual NPI and BPRS scales are generally weak indicating that sub-scales on the two instruments showed poor agreement in this

population, the putative accuracy overall of these observations is supported by the results not being influenced by other variables such as age or sex; and the concordance between NPI and BPRS global ratings of psychopathology described below. Further, the patterns of psychopathology identified with these instruments are consistent with the published literature, the triad of agitation, irritability and apathy/depression identified on NPI, characteristic of the inter-ictal dysphoric disorder of epilepsy (Blumer, 2000), and symptoms such as dysphoria, anxiety, somatic concern, rated highly in the BPRS, widely reported in epilepsy (Lambert & Robertson, 1999). The patterns of psychopathology identified in this study therefore are generally comparable with other studies in similar populations with refractory epilepsy. These findings also highlight the pre-eminence of co-morbid psychopathology in populations with refractory epilepsy.

Overall, however, with the NPI appearing to consistently outperform the BPRS in this study, greater emphasis needs to perhaps be placed on the findings from that instrument, rather than the BPRS.

7.2.2.6 Comparing Behavioural Domains in Cognitively Impaired and Cognitively Unimpaired Persons with Epilepsy

We took MMSE scores as overall measures of cognitive impairment in this study. There were nearly twice as many cognitively impaired subjects as there were cognitively unimpaired subjects.

There were no differences between cognitively impaired and cognitively unimpaired groups in terms of age, reflecting perhaps the generic nature cognitive impairment in this population. That there were no age or sex differences between the groups also indicates that the difference in psychopathology scores between cognitively impaired and unimpaired groups is a true difference, not influenced by these potential confounders. That both measures of psychopathology, NPI and BPRS demonstrate differences, albeit with different degrees of significance, provides support overall to the validity of these findings.

While both NPI and BPRS scores were significantly different between the two groups, the difference in BPRS scores was greater when compared to the NPI scores. The NPI has provided more consistent results in all the prior analysis described herein, and in this instance too the confidence intervals of the difference in means are wider with BPRS ratings than with NPI ratings. However, even as rated by the NPI, there is a significant difference in the psychopathology scores between cognitively impaired and unimpaired groups. This is in line with prediction, a greater burden of psychopathology in cognitively impaired subjects being expected. The finding appears relatively robust, as it is demonstrated with two competing measures, carer and observer rated, and is unlikely to be a chance association.

While sources of bias: selection, recall, and observer do exist, as reviewed earlier in this section, these appear unlikely to influence any more than already stated, the demonstrated differences between cognitively impaired and cognitively unimpaired groups. Potential confounders like age and sex have been accounted for. However, we have limited descriptive data available, due to limited resources

available to this study, and have not therefore accounted for all sources of confounding. As mentioned earlier in this section, the possibility of reverse causality, influencing these results remains. However, the association between cognitive impairment (both learning disability and dementia) and psychopathology is one that has been well established (Deb & Hunter, 1991 a & b; Krishnamoorthy, 2003a for review), and the current findings are therefore fully understandable in the context from which they emerge.

Cognitive impairment in this study was however established using the MMPI, may have been state or trait, and may have been developmental or acquired, distinctions which are important, as has been highlighted recently (Besag, 2001).

7.2.2.7. Psychiatric Co-morbidity in the Cognitively Unimpaired Subgroup: Comparative Analysis of Measures

When clinical significance ratings and ICD-10 diagnostic categories were compared, there were significant differences between the two ratings, clinical significance ratings yielding a higher prevalence of psychopathology. In this sample too, as with the primary care sample, there was limited agreement between the NBI patient and carer scales, and this was restricted to key indices of psychopathology that are over-represented in epilepsy. When the different measures employed in the study, NPI (carer rated), BPRS (expert-observer), NBI (epilepsy specific) were compared with the two gold standards of clinical significance and ICD-10 diagnosis using ROC analysis, some interesting observations merged. No instrument appeared to perform well against either gold standard, the performances being roughly comparable and

generally poor. The cut-off scores were low, and the sensitivity and specificity scores they yielded poor.

This generic failure of instruments to agree with one another may be explained in a number of ways.

1. The sources of information for each instrument are clearly different, professional carer, expert observer and self-ratings all being employed in different instruments. Such a variety of sources attempting to measure a common psychopathology construct is probably inherently unworkable.
2. The nature of the instruments employed in this study, the NPI (developed primarily for neurodegenerative disorders specifically dementia where the patient is unable to give reliable information about his or her status); the BPRS (developed for populations with psychoses usually quite severe with a number of positive and negative signs); the NBI (an epilepsy specific measure of psychopathology that examines existential and philosophical issues and opinions, making it most suitable for application in educated and unimpaired populations with epilepsy), may have inherent limitations when applied to an institutional population with epilepsy.
3. Given their status as institutional residents, with reduced exposure to the outside world, generally low levels of education, and probably with decreased ability to perceive correctly abstract concepts such as emotions and feelings, it is in some ways not

surprising that the cognitively unimpaired group when interviewed using the PSE components of the SCAN interview, appeared to provide inconsistent responses. The high prevalence of symptoms reported in the PSE contrast with the prevalence of ICD-10 psychiatric diagnosis. The PSE clinical significance was based on a positive rating on one symptom category, and it is multiplicity of symptoms that usually results in criteria for diagnosis, thus explaining the divergence of ratings using these two approaches. Another possibility of course would arise due to the highly controlled and supportive nature of the institutional setting, resulting in subjects experiencing symptoms, but not perceiving disablement as a consequence of these, disablement being an important aspect of criteria based diagnosis.

7.3. Use of the NPI in Institutional Populations with Epilepsy

In this study the NPI has emerged as viable carer rated instrument that may be applied in institutional populations with epilepsy. The instrument appears to have good content validity as revealed by the exploratory factor analysis, and good concurrent validity at least for psychiatric caseness with instruments such as the BPRS. The failure of the NPI to agree with more established instruments of psychopathology (gold standard measures) used in population based studies such as the PSE/SCAN and ICD-10 derived criteria thereof, may be more a reflection of the poor suitability of such measures in institutional populations with high levels of cognitive impairment, as opposed to poor

performance of the NPI in these populations. Indeed, it may be argued that the NPI is the more appropriate instrument for application in studies involving cognitively impaired patients with epilepsy. The NPI also has the advantage that it may be applied in both learning disabled patients and those with acquired cognitive impairment.

The prospective use of the NPI to assess caregiver rated psychopathology in these settings will:

- Help in identifying more subjects with hitherto unidentified behavioural disturbance
- Aid in assessing the need for specialist mental health services for patients with epilepsy, the learning disabled and those in residential care in particular
- Aid in the rehabilitation process
- Provide data in support of the need for improved mental health service provision in these settings
- Perhaps most importantly, improve outcome for people with epilepsy in residential care

7.4. Integrating Discussion, Conclusions & Recommendations for Future Research:

These studies have shown that a considerable burden of psychopathology exists in epilepsy, both in primary care and in institutional populations. The precise prevalence figures appear to vary depending on the instruments employed, as has

been amply demonstrated in the review sections of this thesis. Importantly, the primary care study has demonstrated quite unequivocally that subjects with epilepsy have a significantly greater prevalence and burden of psychopathology than their peers in the community. The institutional study also reveals a greater burden of psychopathology in cognitively impaired individuals, when compared with their cognitively unimpaired peers. Given the significant co-morbidity that exists between epilepsy, learning disability and psychiatric illness in the community, the results in a relatively stable institutional population are of considerable relevance. Overall, these data underline the importance of psychiatric co-morbidity in epilepsy, in public health terms. Future studies, interventions and the planning and development of services for epilepsy clearly need to address psychiatric co-morbidity within their remit.

So what if patients with epilepsy have a greater burden of co-morbid psychopathology than their peers? Surely it is control of seizures that is paramount for their well being? While a small number of studies have addressed this issue using sophisticated statistical techniques (Jacoby et al, 1996; Baker et al, 1996) our primary care study is unique in having made detailed head to head comparisons across a range of measures, albeit in a small but representative population. It is apparent that psychiatric co-morbidity has a greater impact on disablement than seizure severity, and this finding is remarkably consistent across measures of psychological burden employed in this study. While seizure severity is undeniably an important outcome measure, and a predictor of well being for patients with epilepsy, it is clear that psychological morbidity is an equally if not more important a predictor of outcome in this chronic and disabling illness. It

seems clear therefore that future studies of outcome in epilepsy must employ reliable and valid measures of psychiatric co-morbidity, in addition to measures of seizure frequency and severity, and measures of disablement.

A question that has bogged researchers in this arena is "which measure" resulting in a plethora of poorly validated measures being employed. We have for probably the first time compared a range of measures screening, diagnostic, generic and epilepsy specific, in a primary care population. Examining the results it becomes apparent that screening measures such as the HADS and GHQ perform well when compared with established gold standards. We have presented herein cut off scores for these measures based on the best match of sensitivity and specificity. The HADS consistently outperformed the GHQ in this study in a range of comparisons. Although originally developed for the assessment of hospital patients (Zigmond & Snaith, 1983), this instrument has shown itself to be good at assessing symptom severity and caseness of anxiety and depression, in a number of different populations (Bjelland et al, 2002). It is not surprising therefore that in a population of individuals with a chronic illness, it outperforms the scaled GHQ-28. Interestingly, a number of epidemiological studies in the UK (Jacoby et al, 1996; O'Donoghue et al, 1999) have employed the HADS as a measure of psychological morbidity, but have used the published cut-off score of 11. The study reported here reveals lower cut-off scores as being more sensitive markers of caseness, a factor which future studies must explore.

It is clear from our study that the CIS-R is superior to the HADS and GHQ when compared to the ICD-10 and clinical significance gold standards. However,

the CIS-R is an instrument that is more cumbersome than the HADS to employ, and takes longer to complete. Indeed the self-report version is computer based and necessitates the use of a portable computer. The marginal advantages that the CIS-R enjoys in relation to the HADS and GHQ are likely to be sacrificed in the altar of response and non-completion rates, essential requirements for most epidemiological studies. Indeed, there is evidence from the National Psychiatric Morbidity Surveys that the CIS-R suffers from pragmatic constraints in this setting, researchers in that study having to abandon it in favour of the GHQ, following initial sample collection and feedback thereof (Jenkins et al, 1998).

The other instrument that has yielded interesting results in our study is the NBI, the only epilepsy specific measure in existence, to our best knowledge, and one that has never been subject to rigorous psychometric testing. While the prevalence of epilepsy specific psychopathology variables is generally high as rated on this measure, it is interesting that the patient total scale scores appeared to be a good measure of generic psychiatric caseness, providing evidence of this measures concurrent validity. However, the carer scale proved to be unhelpful in discriminating psychiatric cases from non-cases, and compared poorly with measures across the board. Our study was not adequately powered to explore the internal consistency of the NBI. With 100 patient and 100 carer items, the scale is likely to have a number of overlapping and redundant items all of which relate to a limited number of constructs. An exploratory factor analysis of this measure needs to be undertaken, and with the large number of items, the rule of thumb dictates a sample of at least 1000 subjects (10/item) (Tabachnik & Fiddell, 2000).

The BPRS proved to be less than robust in the present study, failing to yield either evidence of good internal consistency, or indeed evidence of concurrent validity. However, the NPI, while failing in concurrent validity tests with the gold standard measures, yielded a reliable and interpretable four-factor solution, that appeared to have clinical correlates. With the relative paucity of gold standard carer rated measures that may be employed in learning disabled, otherwise cognitively impaired, or institutionalised populations with epilepsy (see Kerr et al & Espie et al, 1997 for example) the NPI may prove to be a useful carer rated measure of psychopathology in epilepsy. Indeed, the failure may not be that of the NPI; it may be the failure of the so-called gold standard measures to provide valid data in an institutional population. The performance of the NBI in this population also left much to be desired, highlighting the need to identify valid and reliable measures that may be employed in studies at this interface.

Which brings us to the interesting question of what the gold standard should be in these settings. Two contrasting gold standard measures have been used for comparison with the range of instruments both studies. The ICD-10 criteria based measure of psychiatric caseness is the more straightforward of the two. These international criteria were developed by the WHO and are now in their tenth edition (WHO, 1992a). These criteria arose from original research efforts across a number of centres worldwide, as well as a consultation process that involved experts from across the globe. The ICD-10 criteria were also somewhat influenced by DSM criteria from the United States of America. Although intending to be a framework of guidelines that aid clinical diagnosis and attempt to bring uniformity to psychiatric diagnosis across the globe, criteria such as these, have

perhaps due to their specific nature, achieved exalted status in clinical and epidemiological psychiatric research, and are relied upon to discriminate psychiatric cases from non-cases.

However, this ideal of criteria based diagnosis does in several situations leave much to be desired. Transcultural settings where conventional rules may fail to apply are one example (Ustun & Sartorius, 1995). Disorders such as epilepsy in which the burden of psychopathology is high, and may not fulfil conventional criteria, another (Krishnamoorthy 2000, 2001). Indeed, Trimble (1991) and Blumer (1999) have among others elegantly described a psychopathology that is unique, distinct and specific to epilepsy.

In settings such as these it is believed that the development and use of special operational rules may well be the solution (Prince, 1998). Indeed, even prestigious international collaborative epidemiological studies such as the "WHO Study of Psychological Problems in Primary Health Care" (Ustun & Sartorius, 1995) have relied on this approach. In the current study, given the perceived burden of sub-clinical psychological morbidity in epilepsy that fails to meet conventional criteria for caseness, we operationalised a system of rating clinical significance, that relied upon the PSE interview, and used symptom load and attendant disablement as the base criteria. Interestingly, this approach appeared to yield dividends, not just by diagnosing a greater burden of psychopathology than that identified by ICD, but also by demonstrating better concurrent validity across the range of measures employed. Interestingly also, this measure of caseness appeared to outperform the ICD diagnosis measure as a predictor of disablement. Not surprisingly, the WHO

study referred to herein also found better agreement between the screening measures employed and clinician ratings of caseness when compared to the so called gold standard of criteria based diagnosis.

It may be argued on the one hand, that this result is but expected. Clinical significance ratings are like the other measures used in this study for comparison, primarily symptom based, and thus more likely to demonstrate agreement. On the other, the consistency of these observations, and the link with disablement, further considerably the argument that epilepsy neuropsychiatrists have often put forward, in favour of a sub-clinical burden of psychopathology that fails to meet conventional criteria, but is nevertheless disabling.

While arguments have recently been put forward in favour of doing away with the clinical significance ratings in DSM-IV (Spitzer & Wakefield, 1999), we propose that these are merely the reflection of established "criteriologists" digging their heels in, unwilling to change. Based on our findings, we choose to take the opposite view, at least in epilepsy, that clinical significance ratings arising from clinician administered semi-structured interviews, and following operational rules have the potential to be robust measures of caseness (Williams et al, 2002), perhaps with greater validity than arbitrary criteria that have resulted from international consensus (and compromise).

As Prince (1998) has elegantly put it, the argument in psychiatric epidemiology must move from "is it a case?" to "a case for what?" The studies described in this thesis have in our belief provided the evidence for clinical researchers in the epilepsy arena to make this paradigm shift, leading to more meaningful and clinically relevant data in the years to come.

8. REFERENCES

Aarsland D, Larsen JP, Lim NG, Janvin C, Karlsen T, Tandberg E, Cummings JL. (1999). Range of neuropsychiatric disturbances in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 67: 492–496.

Adams F. (1939). *The Genuine Works of Hippocrates.* Baltimore: Williams & Wilkins (Cited in Trimble, 1991).

Allen MH, Currier GW, Hughes DH, Reyes-Harde M, Docherty JP. (2001). The Expert Consensus Panel for Behavioural Emergencies. The Expert Consensus Guideline Series. Treatment of behavioural emergencies. *Postgrad Med* May: 1–88.

Aman MN, Singh NN, Stewart AW, Field CJ. (1985). The aberrant behaviour checklist: a behaviour rating scale for the assessment of treatment effects. *Am J Ment Def* 89: 485–491.

American Psychiatric Association (1952). *Diagnostic and Statistical Manual; Mental Disorders.* Washington, DC: American Psychiatric Association.

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders, DSM-IV.* Washington, DC: American Psychiatric Association.

Andrews DJ, Reiter JM, Schonfeld W, Kastl A, Denning, PA. (2000). Neurobehavioral treatment for unilateral complex partial disorders: a comparison of right- and left-hemisphere patients. *Seizure* 9: 189–197.

Angst J. (1998). The emerging epidemiology of hypomania and bipolar disorder. *J Affect Disord*; 50(2–3): 143–151.

Anhoury S, Brown RJ, Krishnamoorthy ES, Trimble MR. (2000). Psychiatric outcome following temporal lobectomy: a predictive study. *Epilepsia* 41(12): 1608–1615.

Annegers JF, Hauser WA, Elveback LR. (1979). Remission of seizures and relapse in patients with epilepsy. *Epilepsy* 20: 729–737.

Annegers JF, Grabow JD, Groover RV, Laws ER, Elveback LR, Kurland LD. (1980). Seizures after head trauma: a population study. *Neurology* 30: 683–689.

Annegers JF, Hauser WA, Anderson VE, Kurland LT. (1982). The risks of seizure disorder among relatives of patients with childhood epilepsy. *Neurology* 32: 174–179.

Anthony JC, LeResche L, Niaz U, vonKorff MR, Folstein MF (1982). Limits of the "Mini Mental State" as a screening test for dementia and delerium among hospital patients. *Psychol Med* 12(2): 397-408.

Baker GA, Jacoby A, Chadwick DW. (1996). The associations of psychopathology in epilepsy. *Epilepsy Res* 25: 29–39.

Baker GA, Brooks J, Buck D, Jacoby A (1998a). The stigma of epilepsy: a European perspective. *Epilepsia* 41(1): 98–104.

Baker GA, Gagnon D, McNulty P. (1998b). The relationship between seizure frequency, seizure type and quality of life: findings from three European countries. *Epilepsy Res* 30(3): 231–240.

Bartlett JEA. (1957). Chronic psychosis following epilepsy. *Am J Psychiat* 114: 338.

Bear DM, Fedio P. (1977). Quantitative analysis of interictal behaviour in temporal lobe epilepsy. *Arch Neurol* 34: 454–467.

Bear DM. (1979). Temporal lobe epilepsy – a syndrome of sensory-limbic hyperconnection. *Cortex* 15(3): 357–384.

Bebbington P, Nayani T. (1995). The psychosis screening questionnaire. *International Journal of Methods in Psych Res* 5: 11–19.

Beck AT. (1993). Cognitive therapy: past, present, and future. *J Consult Clin Psychol* 61(2): 194–198.

Berg AT, Shinnar S. (1991). The risk of recurrence following a first unprovoked seizure: a quantitative review. *Neurology* 41: 965–972.

Berg AT, Shinnar S.(1994). Relapse following discontinuation of AEDs: a meta-analysis. *Neurology* 44: 601–608.

Besag FM. (2001). Treatment of state-dependant learning disability. *Epilepsia* 42(Suppl. 1): 52–54.

Besag FM. (2003). The Treatment of Psychiatric Disorders in Epilepsy. Lecture delivered at the Bethel–Cleveland International Epilepsy Symposium, Bielefeld.

Betts T. (2002). Non-epileptic seizures (pseudoseizures) In: Duncan JS, Sidodiya SM, Smalls JE, eds. *Epilepsy 2002: From Science to Patient, Lecture Notes.* International League Against Epilepsy London, pp. 241–256.

Bharucha NE, Bharucha EP, Bharucha AE, Bhishe AV, Schoenberg BS. (1988). Prevalence of epilepsy in the Parsi community of Bombay. *Epilepsia* 29: 111–115.

Bjelland I, Dahl AV, Haug TT, Neckelmann D. (2002). The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 52: 69–77.

Blumer D. (1995). Personality disorders in epilepsy. In: Ratey JJ, ed. *Neuropsychiatry of Personality Disorders.* Boston: Blackwell Science, pp. 230–263.

Blumer D. (1995). The neurobehavioral inventory: personality disorders in epilepsy. In: Ratey JJ, ed. *Neuropsychiatry of Personality Disorders.* Boston: Blackwell Science, pp. 230–263.

Blumer D. (2000). Dysphoric disorders and paroxysmal effects: recognition and treatment of epilepsy-related psychiatric disorders. *Harvard Rev Psychiatr* 8(1): 8–17.

Bonhoeffer K. (1909). Zur Frage der exogenen Psychosen. *Neurol Zbl* 32: 499–505 (Cited in Schmitz, 1998).

Borkovec TD, Costello E. (1993). Efficacy of applied relaxation and cognitive-behavioural therapy in the treatment of generalized anxiety disorder. *J Consult Clin Psychol* 61: 611–619.

Boudreault M, Thivierge J, Coter R, Boutin P, Julien Y, Bergeron S. (1988). Cognitive development and reading achievement in pervasive-ADD, situational-ADD, and control children. *J Child Psychol and Psychiat* 29: 611–619.

Bredkjaer SR, Mortensen PB, Parnas J. (1998). Epilepsy and non-organic non-affective psychosis- National Epidemiologic Study. *Br J Psychiat* 172: 235–238.

Brodie MJ, French JA. (2000). Management of epilepsy in adolescents and adults. *The Lancet* 356(9226): 323–329.

Brodie MJ, Sander JW. (2002). Overview of established antiepileptic drugs. In: Duncan JS, Sidodiya SM, Smalls JE, eds. *Epilepsy 2002: From Science to Patient*. Lecture Notes. London: International League Against Epilepsy, pp. 279–292.

Brown RJ, Trimble MR. (2000). Dissociative psychopathology, non-epileptic seizures and neurology (Editorial). *J Neurol Neurosurg Psychiatry* 69: 285–291.

Brugha TS, Jenkins R, Taub N, Meltzer H, Bebbington PE. (2001). A general population comparison of the Composite International Diagnostic Interview (CIDI) and the Schedules for Clinical Assessment in Neuropsychiatry (SCAN). *Psychol Med* 31(6): 1001–1013.

Bruton CJ. (1988). *The Neuropathology of Temporal Lobe Epilepsy*. Oxford: Oxford University Press.

Burke WJ, Wengel SP (2003). Late-life mood disorders. *Clin. Geriatr Med.* 19(4): 777-97.

Camfield C, Camfield P. (1994). Epidemiology of epilepsy in children less than 16 based on a regional population. *Epilepsia* 35(Suppl. 8): 149.

Campbell DT, Fiske DW (1959). Convergent and discriminant validation by the multitrait multimethod matrix. *Psychol Bull* 56(2): 81-105.

Capes L, Moore BC. (1970). Behaviour differences between seizure and non-seizure retardates. *Arizona Med* 27: 74–76.

Caplan R, Shields WR, Mori L, Yudovin S. (1991). Middle childhood onset of interictal psychosis. *J Am Acad Child Adolesc Psychiatry*, 30: 893–896.

Carpio A, Hauser WA. (1993). The distribution and etiology of epilepsy in the tropics of America. *Rev Ecuat Neurol* 2: 137–145 (Cited in Hauser, 1998).

Centorrino F, Price BH, Tuttle M, Bahk WM, Hennen J, Albert MJ, Baldessarini RJ. (2002). EEG abnormalities during treatment with typical and atypical antipsychotics. *Am J Psychiatry* 159(1): 109–115.

Chandra V, Bharucha NE, Schoenberg BS et al. (1984). National mortality data for death due to and all death due to epilepsy in the United States. In: Porter RJ, ed. *Advances in Epileptology*. Vol. 15. New York: Raven Press.

Cockerell OC, Moriarty J, Trimble MR, Sander JWAS, Shorvon SD. (1996). Acute psychological disorders in patients with epilepsy: a nation-wide study. *Epilepsy Research* 25: 119–131.

Collins English Dictionary (1994). London, William Collins & Sons.

Commission on Classification and Terminology of the International League Against Epilepsy (1981). Proposal for revised clinical and electroencephalographic

classification of epileptic patients in everyday neurological practice. *Epilepsia* 22: 489–501.

Commission on Classification and Terminology of the ILAE (1989). Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 30: 389–399.

Commission on Epidemiology and Prognosis, International League Against Epilepsy (1993). *Epilepsia* 34(4): 592–596.

Cooper JE, Kendall RE, Gurland BJ, Sharpe L, Copeland JRM, Simon R. (1972). *Psychiatric Diagnosis in New York and London: A Comparative Study of Mental Hospital Admissions.* London: Oxford University Press.

Copeland JRM (1989). Rating Scales for Cognitive Impairment. In: Thompson C, ed. *The Instruments of Psychiatric Research.* Chichester: John Wiley & Sons.

Corbett JA. (1981). Epilepsy and mental retardation. In: Trimble MR, Reynolds EH, eds. *Epilepsy and Psychiatry.* Edinburgh: Churchill Livingstone, pp. 138–146.

Corbett JA. (1988). Epilepsy and mental handicap. In: Laidlaw J, Richens A, Oxley J, eds. *A Textbook of Epilepsy.* Edinburgh: Churchill Livingstone, pp. 533–558.

Cramer JA (2001). Assessing the severity of seizures with epilepsy: which scales are valid? *Curr Opin Neurology* 14(2): 225-9.

Cramer JA, Fisher R, Ben-Menachem E, French JA, Mattson RH. (1999). New antiepileptic drugs: comparison of key clinical trials. *Epilepsia* 40: 590–620.

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. (1994). The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 44: 2308–2314.

Cummings JL. (1997). The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology* 48(5 Suppl. 6): S10–S16.

Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology* 48(5)(Suppl 6): S10–S16.

Currie S, Heathfield KWG, Henson RA, Scott DF. (1971). Clinical Course and Prognosis of Temporal Lobe Epilepsy – A Survey of 666 Patients. *Brain* 94: 173–190.

Czobor P, Volavka J (1996). Dimensions of the Brief Psychiatric Rating Scale: an examination of stability during haloperidol treatment. *Compr. Psychiatry* 37(3): 205-15.

Dalrymple J, Appleby J. (2000). Cross sectional study of reporting of epileptic seizures to general practitioners. *BMJ* 320(7227): 94–97.

Deb S, Cowie VA, Richens A. (1987). Folate metabolism and problem behaviour in mentally handicapped epileptics. *J Ment Def Res* 31: 163–168.

Deb S, Hunter D. (1991a). Psychopathology of People with mental handicap and epilepsy. I: maladaptive behaviour. *Br J Psych* 159: 822–826.

Deb S, Hunter D. (1991b). Psychopathology of people with mental handicap and epilepsy. II: psychiatric illness. *Br J Psych* 159: 826–830.

Deb S, Hunter D. (1991c). Psychopathology of people with mental handicap and epilepsy. III: personality disorder. *Br J Psych* 159: 830–834.

Department of Health (1999). Services for Patients with Epilepsy. Report of the Clinical Standards Advisory Group, Dept. of Health.

Devinsky O, Vasquez B. (1993). Behavioural changes associated with epilepsy. *Neurol Clin* 11: 127–149.

Devinsky O, Najjar S (1999). Evidence against the existence of a temporal lobe epilepsy personality syndrome. *Neurology* 53 (5 Suppl. 2): S13-25.

Diaz F, Garcia RH, Gilman RH, Gonzales AE, Castro M, Tsang VC, Pilcher JB, Vasquez LE, Lescano M, Carcano C et al. (1992). Epidemiology of taeniasis and cysticercosis in a Peruvian village. *Am J Epidemiol* 145: 875–882.

Diaz-Olavarrieta C, Cummings JL, Velazquez J, Garcia de la Cadena C. (1999). Neuropsychiatric manifestations of multiple sclerosis. *J Neuropsychiatry Clin Neurosci* 11: 51–57.

Dick JP, Guiloff RJ, Stewart A, Blackstock J, Bielawaska C, Paul EA, Marsden CD (1984). *J Neurol Neurosurg Psychiatry* 47(5): 496-9.

Dichter MA, Brodie MJ. (1996). New antiepileptic drugs. *N Engl J Med* 334: 1583–1590.

Dikmen S Hermann BP, Wilensky AJ Rainwater G. (1983). Validity of the Minnesota Multiphasic Personality Inventory (MMPI) to psychopathology in patients with epilepsy. *J Nerv Ment Dis* 171(2): 114–122.

Dodrill CB, Batzell LW. (1986). Interictal behavioural features of patients with epilepsy. *Epilepsia* 27(Suppl. 2): S64–S76.

Dohrenwend BP. (1995). The problem of validity in field studies of psychological disorders, revisited. In: Tsuang MT, Tohen M, Zahner GEP, eds. *Textbook of Psychiatric Epidemiology*. New York: Wiley-Liss, pp. 3–22.

Dongier S. (1959/60). Statistical study of clinical and electroencephalographic manifestations of 536 psychotic episodes occurring in 516 epileptics between clinical seizures. *Epilepsia* 1: 117–142.

Duncan JS, Sander JW (1991). The Chalfont Seizure Severity Scale. *J Neurol Neurosurg Psychiatry* 54(10): 873-6.

Edeh J, Toone B. (1987). Relationship between interictal psychopathology and the type of epilepsy. *Br J Psychiat* 151: 95–101.

Elger G, Hoppe C, Falkai P, Rush AJ, Elger CE. (2000). Vagus nerve stimulation is associated with mood improvements in epilepsy patients. *Epilepsy Res* 42(2–3): 203–210.

Engel J Jr, Wilson C, Lopez-Rodriguez F. (2002). Limbic connectivity: anatomical substrates of behavioural disturbances in epilepsy. In: Trimble MR, Schmitz B, eds. *The Neuropsychiatry of Epilepsy.* Cambridge: Cambridge University Press, pp. 18–40.

Espie CA, Montgomery JA, Gillies JB. (1988). The development of a psychosocial behaviour scale for the assessment of mentally handicapped people. *J Ment Def Res* 32: 395–403.

Espie CA, Kerr M, Paul A, O'Brien G, Betts T, Clark J, Jacoby A, Baker, G. (1997). Learning disability and epilepsy. 2. A review of available outcome measures and position statement on development priorities. *Seizure* 6: 337–350.

Eyman RK, Capes L, Moore BC et al. (1969). Retardates with seizures. *Am J Ment Def* 74: 651–59.

Feighner JP, Robins B, Guze SB, Woodruff RA Jr, Winokur G, Munoz R. (1972). Diagnostic criteria for use in psychiatric research. *Arch Gen Psychaitry* 26: 57–63.

Feksi AT, Kaamugisha J, Sander JW, Gatiti S, Shorvon SD. (1991). Comprehensive primary health care AED treatment programme in rural and semi-rural Kenya. *Lancet* 337: 406–409.

First Seizure Trial Group (1993). Randomized clinical trial on the efficacy of AEDs in reducing the risk of relapse after a first unprovoked tonic-clonic seizure. *Neurology* 43: 478–483.

Fisher RS, Vickrey BG, Gibson P, Hermann B, Penovich P, Scherer A, Walker S. (2000). The impact of epilepsy from the patient's perspective I. Descriptions and subjective perceptions. *Epilepsy Research* 41: 39–51.

Flemming CF. (1859). *Pathologie und Therapie der Psychosen.* Berlin: Hirschwald (Cited in Schmitz, 1998).

Flor-Henry P. (1969). Psychosis and temporal lobe epilepsy. *Epilepsia* 10: 363–395.

Flor-Henry P. (1972). Ictal and interictal psychiatric manifestations in epilepsy: specific or non-specific? A critical review of some of the evidence. Epilepsia 13(6): 773–783.

Folstein MF, Folstein SE, McHugh PR. (1975). Mini mental state: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12: 189–198.

Foulds GA, Bedford A. (1975). Hierarchy of classes of personal illness. *Psychological Medicine* 5(2): 181–192.

George MS. (2001). Summary and future directions of therapeutic brain stimulation: neurostimulation and neuropsychiatric disorders. *Epi & Behav* 2: S95–S100.

Geschwind N. (1977). Behavioural change in temporal lobe epilepsy. *Arch Neurol* 34: 453.

Getz K, Hermann B, Seidenberg M, Bell B, Dow C, Jones J, Woodard A, Rutecki P, Sheth R, O'Leary D, Magnotta V (2002). Negative symptoms in temporal lobe epilepsy. *Am. J. Psychiatry* 159(5): 644-51.

Goldberg DP, Cooper B, Eastwood MR, Kedward HB, Shepard M. (1970). A standardised psychiatric interview for use in community surveys. *Br J Preventive Soc Med* 24: 18–23.

Goldberg LR. (1972). Man versus mean: the exploitation of group profiles for the construction of diagnostic classification systems. *J Abnormal Psychol* 79: 121–131.

Goldberg D, Williams P. (1988). *A user's guide to the General Health Questionnaire.* Windsor: NFER-Nelson.

Goldberg D, Huxley P. (1992). *Common Mental Disorders: A Biosocial Model.* London: Tavistock/Routledge.

Goldberg D, Lecrubier Y. (1995). Form and frequency of mental disorders across centres. In: Ustun TB, Sartorius N, eds. *Mental Illness in General Health Care: An International Study*. Chichester: John Wiley and Sons, pp. 323–334.

Goldstein LH. (1990). Behavioural and cognitive-behavioural treatments for epilepsy: a progress review. *Br J Clin Psychol* 29(3): 257–269.

Goodridge DMG, Shorvon SD. (1983). Epilepsy in a population of 6000. *Br Med J* 287: 641–647.

Griesinger W. (1857). *Mental Pathology and Therapeutics.* London: New Sydenham Society (Cited in Trimble, 1991).

Griesinger W. (1869/69). Uber einige epileptoide Zustande. *Arch Psychiatr Nervenkr* 320–333 (Cited in Schmitz, 1998).

Gudmundsson G. (1966). Epilepsy in Iceland – a clinical and epidemiological investigation. *Acta Neurol Scand* 43(Suppl 25): 64–90.

Gureje O. (1991). Interictal psychopathology in epilepsy– prevalence and pattern in a Nigerian clinic. *Br J Psychiat* 158: 700–705.

Hales RE, Hilty DA, Wise MG. (1997). A treatment algorithm for the management of anxiety in primary care practice. *J Clin Psychiatry* 58(Suppl 3): 76–80.

Hamilton M (1967). Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 6(4): 278-96.

Harden CL, Pulver MC, Ravdin LD, Nikolov B, Halper JP, Labar DR. (2000). A Pilot study of mood in epilepsy patients treated with vagus nerve stimulation. *Epilepsy & Behaviour* 1: 93–99.

Harle J. (1729). An historical essay on the state of the physick in the old and the new testament and the apocryphal interval. London (Cited in Trimble, 1991).

Hart YM, Sander JW, Johnson AJ, Shorvon SD. (1990). National General Practice Study of epilepsy: recurrence after a first seizure. *Lancet* 336: 1271–1274.

Hasin DS, Skodol AE. (1989). Standardized diagnostic interviews for psychiatric research. In: Thompson C, ed. *The Instruments of Psychiatric Research.* Chichester: Wiley.

Hauser WA, Annegers JF, Elveback LR. (1980). Mortality in patients with epilepsy. *Epilepsia* 21: 339–412.

Hauser WA, Annegers JF, Kurland LT. (1991). Prevalence of epilepsy in Rochester, Minnesota, 1940–1980. *Epilepsia* 32: 429–445.

Hauser WA, Annegers JF, Kurland LT. (1993). The incidence of epilepsy and unprovoked seizures in Rochester, Minnesota, 1935–1984. *Epilepsia* 34: 453–468.

Hauser AW. (1998). Incidence and prevalence. Epidemiology Section In: Engel J Jr., Pedley TA, Hauser AW et al. eds. *Epilepsy - A Comprehensive Textbook.* Lippincott-Raven: New York (pp. 47–58).

Helzer JE, Robins LN, Croughan JL, Welner A. (1981). Renard diagnostic interview: its reliability and procedural validity with physicians and lay interviewers. *Arch Gen Psychiatry* 38: 393–398.

Hennekens CH, Buring JE. (1987). *Epidemiology in Medicine.* Boston/Toronto: Little Brown.

Hill D. (1953). Psychiatric disorders of epilepsy. *Med Press* 20: 473.

Hirschfeld RMA, Shea MT. (1995). In: Kaplan HI, Saddock BJ, eds.*Comprehensive Textbook of Psychiatry.* 6th edn. Baltimore: Williams & Wilkins, pp. 1179–1189.

Hoffman H. (1859). *Beobachtungen und Erfahrungen uber Seelenstorungen und Epilepsie.* Frankfurt/Main: Rutten (Cited in Schmitz, 1998).

Hoffman F. (1862). Über die Eintheilung der Geisteskrankheiten in Siegburg. *Allg Z Psychiatr* 19: 367–391 (Cited in Schmitz, 1998).

Hollingshead AB, Redlich FC. (1958). *Social Class and Mental Illness.* New York: Wiley.

Hopkins A, Scrambler G. (1977). How do doctors deal with epilepsy? *Lancet* 1: 183–186.

Hopkins A, Garman A, Clarke C. (1988). The first seizure in adult life: value of clinical features, electroencephalography, and computerised tomographic scanning in prediction of seizure recurrence. *Lancet* 1: 721–726.

Howden JC. (1872,1873). The religious sentiments of epileptics. *Journal of Mental Science* 18: 491–497.

Jacoby A, Baker GA, Steen N, Potts P, Chadwick DW. (1996). The clinical course of epilepsy and its psychosocial correlates: findings from a U.K. Community Study. *Epilepsia* 37(2): 148–161.

Jalava M, Sillanpaa M. (1996). Concurrent illnesses in adults with childhood-onset epilepsy: a population-based 35-year follow-up study. *Epilepsia* 37(12): 1155–1163.

Janz D. (1969,1997). *Die Epilepsien: Spezielle Pathologie und Therapie*. Stuttgart: George Thieme Verlag.

Janz D (1998). Episodic changes in mood and psychoses. In: Trimble MR, Schmitz B. *Forced Normalization and Alternative Psychoses of Epilepsy*. Petersfield: Wrightson, pp. 67–76.

Jenkins R, Bebbington P, Brugha T, Farrell M, Gill B, Lewis G, Meltzer H, Petticrew M. (1997a). The National Psychiatric Morbidity Surveys of Great Britain – strategy and methods. *Psychol Med* 27: 765–774.

Jenkins R, Lewis G, Bebbington P, Brugha T, Farrell M, Gill B, Meltzer H. (1997b). The National Psychiatric Morbidity Surveys of Great Britain – initial findings from the Household Survey. *Psychol Med* 27: 775–789.

Jenkins R, Bebbington P, Brugha TS, Farrell M, Lewis G, Meltzer H (1998). British psychiatry morbidity survey. *Brit. J. Psychiatry* 173: 4-7.

Jette AM, Davies AR, Cleary PD, Calkins DR, Rubenstein LV, Fink A, Kosecoff J, Young RT, Brook RH, Delbanco TL. (1986). The Functional Status Questionnaire: reliability and validity when used in primary care. *J Gen Intern Med* 1(3): 143–149.

Johnson MR, Sander JW. (2001). The clinical impact of epilepsy genetics. *J Neurol Neurosurg Psychiatry* 70(4): 428–430.

Kanner AM. (2003). Depression in epilepsy: prevalence, clinical semiology, pathogenetic mechanisms, and treatment. *Biol Psychiatry* 54: 388–398.

Katon W, Ciechanowski P. (2002). Impact of major depression on chronic medical illness. *J Psychosom Res* 53: 859–863.

Katz MM, Secunda SK, Hirschfeld RM, Koslow SH. (1979). NIMH clinical research branch collaborative program on the psychobiology of depression. *Arch Gen Psychiatry* Jul, 36(7): 765–771.

Kellner CH, Bernstein HJ. (1993). ECT as a Treatment for neurologic illness. In: Coffey CE, ed. *The Clinical Science of Electroconvulsive Therapy*. Spiegel D, Series ed. *Progress in Psychiatry*, Number 38, Washington, DC: American Psychiatric Press, pp. 183–212.

Keranen T, Riekkinen PJ. (1993). Remission of seizures in untreated epilepsy. *Br Med J* 307: 483.

Kerr MP, Espie CA. (1997). Learning disability and epilepsy. 1. Towards common outcome measures. *Seizure* 6: 331–336.

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S et al. (1994). Lifetime and 12 month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry* 51: 8–19.

Kessler RC, Wittchen HV, Abelson JM, McGonagle KA, Schwartz N, Kendler KS et al. (1998). Methodological studies of the Composite International Diagnostic Interview in the US National Comorbidity Survey. *Int J Meth Psychiatry Res* 7: 33–35.

Ketter TA, Malow BA, Flamini R, White SR, Post RM, Theodore WH. (1994). Anticonvulsant withdrawal-emergent psychopathology. *Neurology* 44(1): 55–61.

Ketter TA, Post RM, Theodore WH. (1999). Positive and negative psychiatric effects of antiepileptic drugs in patients with seizure disorders. *Neurology* 53(Suppl. 2): S53–S67.

Klenarman P, Sander JW, Shorvon SD. (1993). Mortality of epilepsy: a study of patients in long term care. *J Neurol Neurosurg Psychiatr* 56: 149–152.

Klerman GL, Lavori PW, Rice J, Reich T, Endicott J, Andreasen NC, Keller MB, Hirschfield RM. (1985). Birth-cohort trends in rates of major depressive disorder among relatives of patients with affective disorder. *Arch Gen Psychiatry* 42(7): 689–693.

Klerman GL, Weissmann MM. (1987). Interpersonal psychotherapy and drugs in the treatment of depression. *Pharmacopsychiatry* 20: 3–7.

Kraepelin E. (1923). *Psychiatrie*. 8th ed. Barth: Leipzig (Blumer, personal communication).

Krishnamoorthy ES, Trimble MR. (1999). Forced normalization – clinical and therapeutic relevance. *Epilepsia* 40(Suppl. 10): S57–S64.

Krishnamoorthy ES. (2000a). An approach to classifying neuropsychiatric disorders in epilepsy (editorial). *Epilepsy & Behaviour* 1: 373–377.

Krishnamoorthy ES, Brown RJ, Samuel R, Trimble MR. (2000b). The neuropsychiatric inventory in epilepsy. *Epilepsia* 41(Suppl. Florence): 155.

Krishnamoorthy ES. (2001). Psychiatric issues in epilepsy. *Current Opinion in Neurology* 14(2): 217–224.

Krishnamoorthy ES. (2002a). Neuropsychiatric disorders in epilepsy – epidemiology and classification. In: Trimble MR, Schmitz B, eds. *The Neuropsychiatry of Epilepsy*. Cambridge: Cambridge University Press, pp. 5–17.

Krishnamoorthy ES, Trimble MR, Sander JW, Kanner A (2002b). Forced Normalization at the Interface between Epilepsy and Psychiatry. Epilepsy & Behaviour 3: 3-8

Krishnamoorthy ES (2003a). Neuropsychiatric Epidemiology at the Interface between Epilepsy and Learning Disability. In: Trimble MR (Ed.), *Learning Disability and Epilepsy- An Integrative Approach*: 17-26, London, Clarius Press.

Krishnamoorthy ES. (2003). Treatment of depression in patients with epilepsy: problems, pitfalls and some solutions. *Epilepsy & Behaviour* 4: S46–S54.

Krishnamoorthy ES, Satishchandra P, Sander JWAS. (2003). Research in epilepsy: development priorities for developing nations. *Epilepsia* 44(S1): 5–9.

Krishnamoorthy ES, Trimble MR, Blumer D. The classification of neuropsychiatric disorders in epilepsy – a proposal of the sub-commission on classification of the ILAE Commission on Epilepsy and Psychobiology (submitted to *Epilepsia*).

Kruijshaar ME, Hoeymans N, Bijl RV, Spijker J, Essink-Bot ML (2003). Levels of disability in major depression. Findings from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Journal of Affective Disorders* 77(1): 53-64.

Lambert M, Robertson MM. (1999). Depression in epilepsy: etiology, phenomenology, and treatment. *Epilepsia* 40(Suppl.10): S21–S47.

Lancman M. (1999). Psychosis and peri-ictal confusional states. *Neurology* 53(Suppl. 2): S33–S38.

Landolt H. (1953). Some clinical electroencephalographical correlations in epileptic psychoses (twilight states). *Electroencephalogr Clin Neurophysiol* 5: 121.

Landolt H. (1958). Serial electroencephalographic investigations during psychotic episodes in epileptic patients and during schizophrenic attacks. In: Lorentz de Haas AM, ed. *Lectures on Epilepsy*. Amsterdam: Elsevier, pp. 91–133.

Landsborough D. (1987). St. Paul and temporal lobe epilepsy. *J Neurol Neurosurg Psychiat* 50: 659–665.

Langner T. (1962). A 22 item screening score of psychiatric symptoms indicating impairment. *Journal of Health and Human Behaviour* 11: 169–276 (Cited by Williams et al., 1980).

Langosch JM, Trimble MR. Epilepsy, psychosis and clozapine. Human Psychopharmacology – Clinical and Experimental (in press).

Lathers CM, Schraeder PL. (1990). *Epilepsy and Sudden Death.* New York: Dekker.

Lavy S, Carmon A, Yahr I. (1972). Assessment of clinical and electroencephalographic classification of epileptic patients in everyday neurological practice. *Epilepsia* 13: 498–508.

Leighton DC, Harding JS, Macklin DB, Hughes CC, Leighton JS. Psychiatric findings of the Stirling Country Study. (1963). *Am J Psychiatry* 127: 1021–1026.

Lennox W. (1960). *Epilepsy and Related Disorders*. London: Churchill (Cited in Sander & Shorvon, 1970).

Lewis AJ. (1934). Melancholia: a historical review. *Journal of Mental Science* 80: 1–42.

Lewis G, Pelosi AJ, Araya R, Dunn, G. (1992). Measuring psychiatric disorder in the community: a standardised assessment for use by lay interviewers. *Psychol Med* 22: 465–486.

Lhatoo SD, Johnson AL, Goodridge DM, Macdonald BK, Sander JW, Shorvon SD. (2001). Mortality in epilepsy in the first 11 to 14 years after diagnosis: multivariate analysis of a long-term, prospective, population-based cohort. *Ann Neurol* 49: 310–315.

Li SC, Schoenberg BS, Bolis CL et al. (1985). Epidemiology of epilepsy in urban regions of the People's Republic of China. *Epilepsia* 26: 391–394.

Litvan I, Cummings JL, Mega M. (1998). Neuropsychiatric features of corticobasal degeneration. *J Neurol Neurosurg Psychiatry* 65(5): 717–721.

Logsdail SJ, Toone BK. (1988). Post-ictal psychoses. A clinical and phenomenological description. *Br J Psychiat* 152: 246–252.

Lund J. (1985a). Epilepsy and psychiatric disorder in the mentally retarded adult. *Acta Psychiatr Scand* 71: 557–562.

Lund J. (1985b). The prevalence of psychiatric morbidity in mentally retarded adults. *Acta Psychiatr Scand* 72: 563–570.

MacDonald BK, Cockerell OC, Sander JW, Shorvon SD. (2000). The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the U.K. *Brain* 123: 665–676.

Manchanda R, Schaefer B, McLachlan R, Blume WT, Wiebe S, Girvin JP, Parrent A, Derry PA. (1996). Psychiatric disorders in candidates for surgery for epilepsy. *J Neurol Neurosurg Psychiatry* 61: 82–89.

Mani KS, Rangan G, Srinivas HV, Narendran S. (1993). Natural History of untreated epilepsy: a community based study in Rural South India. *Epilepsia* 34(Supl.2): 166.

Mann AH, Jenkins R, Belsey E. (1981). The twelve-month outcome of patients with neurotic illness in general practice. *Psychol Med* 11: 535–550.

Mann AH, Blizard R, Murray J, Smith JA, Botega N, MacDonald E, Wilkinson G. (1998). An evaluation of practice nurses working with general practitioners to treat people with depression. *Brit J Gen Practice* 48: 875–879.

Marder SR. (1995). Psychiatric rating scales. In: Kaplan HI, Saddock BJ. eds. *Comprehensive Textbook of Psychiatry.* Vol. 1, 6th edn. Baltimore: Williams & Wilkins, pp. 619–626.

Matsuura M, Adachi N, Oana Y, Okubo Y, Hara T, Onuma T. (2000). A proposal for a new five-axial classification scheme for psychoses of epilepsy. *Epilepsy Behav* 1: 343–352.

Mattson RH, Cramer JA, Collins JF, Smith DB, Delgado-Escueta AV, Browne TR, Williamson PD, Treiman DM, McNamara JO, McCutchen CB et al. (1985). Comparison of carbamazepine, phenobarbital, phenytoin and primidone in partial and secondarily generalised seizures. *N Engl J Med* 313: 145–151.

McConnell HW, Duncan D. (1998). Treatment of psychiatric co-morbidity in epilepsy. In: McConnell HW, Snyder PJ, eds. *Psychiatric Co-morbidity in Epilepsy: Basic Mechanisms, Diagnosis, and Treatment.* Am. Psych. Press.

Mead R. (1746). De Imperio Solis Ac Lunae in Corpora Humani, et Morbis inde Oriundis. London (Cited in Trimble, 1991).

Meduna L. (1935). Versuche uber die biologische Beeinflussung des Ablaufes der Schizophrenic. I. Campher-und Cardiazol-Krampfe. *Z ges Neurol Psychiatr* 152: 235–262.

Mendez MF, Cummings JL, Benson DF. (1986). Depression in epilepsy: Significance and phenomenology. *Arch Neurol* 43: 766–770.

Mendez MF, Grau R, Doss RC, Taylor JL. (1993). Schizophrenia in epilepsy: seizure and psychosis variables. *Neurology* 43: 1073–1077.

Menkes JH, Sankar R (2000). Paroxysmal Disorders. *In: Menkes JH & Sarnat HB (Eds). Child Neurology*. Sixth Edition, pp. 919-995, Philadelphia, Lippincott Williams & Wilkins.

Mielke J, Sebit M, Adamolekun B. (2000). The impact of epilepsy on the quality of life of people with epilepsy in Zimbabwe: a pilot study. Seizure 9: 259–264.

Miller FJW, Court SDM, Walton WS, Know EG. (1960). *Growing up in Newcastle-upon-Tyne. A Continuing Study of Health and Illness in Young Children with their Families*. London: Oxford Press.

Miller DD. (2000). Review and management of Clozapine side effects. *J Clin Psychiatry* 61(Suppl 8): 14–17.

Morrell MJ, Pedley TA. (2000). "The Scarlet E" – Epilepsy is still a burden. *Neurology* 54: 1882–1883.

Moss S, Patel P, Prosser H, Goldberg D, Simpson N, Rowe S, Lucchino R (1993). Psychiatric morbidity in older people with moderate and severe learning disability. I:

Development and reliability of the patient interview (PAS-ADD). *Brit. J. Psychiatry* 163: 471-80.

MRC Antiepileptic Drug Withdrawal Group (1991). Randomised study of antiepileptic drug withdrawal in patients in remission. *Lancet* 337: 1175–1180.

Murray CJL, Lopez AD, eds. (1996). *The Global Burden of Disease*. Boston: Harvard Univ. Press.

Nelson A, Fogel BS, Faust D (1986). Bedside cognitive screening instruments. A critical assessment. *J. Nerv. Ment. Dis* 174(2): 73-83.

Newsom-Davis I, Goldstein LH, Fitzpatrick D. (1998). Fear of seizures – an investigation and treatment. *Seizure* 7: 101–106.

Norman GR, Streiner DL. (2000). *Biostatistics: The Bare Essentials*. London: BC Decker, pp. 163–177.

O'Brien G. (1996). A comparative study of young children and adults with Fragile X syndrome. *Genetic Counselling* 7: 167.

O'Donoghue MF, Duncan JS, Sander JW. (1996). The National Hospital Seizure Severity Scale: a further development of the Chalfont Seizure Severity Scale. *Epilepsia* 37: 563–571.

O'Donoghue MF, Duncan JS, Sander JWAS. (1998). The subjective handicap of epilepsy – a new approach to measuring treatment outcome. *Brain* 121: 317–343.

O'Donoghue MF, Goodridge DMG, Redhead K, Sander JWAS, Duncan JS. (1999). Assessing the psychosocial consequences of epilepsy: a community based study. *Brit J Gen Pract* 49: 211–214.

Olafsson E, Hauser WA, Ludvigsson P, Gudmundsson G. (1996). Incidence and prevalence of epilepsy in rural Iceland. *Epilepsia* 37(10): 951–955.

Olsson I, Steffenberg S, Gilberg C. (1988). Epilepsy and autism and autistic-like conditions: a population-based study. *Arch Neurol* 45: 666–668.

Ormel J, Costa E, Silva JA. (1995). The impact of psychopathology on disability and health perceptions. In: Ustun TB, Sartorius N, eds. *Mental Illness in General Health Care: An International Study*. Chichester: John Wiley and Sons, pp. 335–346.

Overall JE, Gorham DR. (1962). The brief psychiatric rating scale. *Psychol Rep* 10: 799–812.

Perini GI. (1986). Emotions and personality in complex partial seizures. *Psychother Psychosom* 45(3): 141–148.

Perrine K, Kiolbasa T. (1999). Cognitive deficits in epilepsy and contribution to psychopathology. *Neurology* 53(Suppl. 2): S39–S48.

Piazzini A, Canevini MP, Maggiori G, Canger R (2001). The perception of memory failures in epilepsy. *Eur. J. Neurology* 8(6): 613-20.

Placencia M, Shorvon SD, Paredes V, Bimos C, Sander JW, Suarez J, Cascante SM. (1992). Epileptic seizures in an Andean region of Ecuador: incidence and prevalence and regional variation. *Brain* 115: 771–782.

Placencia M, Sander JW, Shorvon SD et al. (1993). AED treatment in a community health care setting in Northern Ecuador: a prospective 12 month assessment. *Epilepsy Res* 14: 237–244.

Pond DA. (1957). Psychiatric aspects of epilepsy. *J Ind Med Prof* 3: 1441.

Pond DA, Bidwell BH. (1959/60). A survey of epilepsy in fourteen general practises II. Social and psychological aspects. *Epilepsia* 1: 285–299.

Post RM. (1995). Mood disorders: somatic treatments. In: Kaplan HI, Saddock BJ eds. *Comprehensive Textbook of Psychiatry*, 6th ed. Baltimore: Williams & Wilkins, pp. 1152–1178.

Post RM, Ketter TA, Denicoff K, Pazzaglia PJ, Leverich GS, Marangell LB, Callahan AM, George MS, Frye MA. (1996). The place of anticonvulsant therapy in bipolar illness. *Psychopharmacology (Berl.)* 128(2): 115–129.

President's Commission on Mental Health (1978). Report to the President from the President's Commission on Mental Health. Washington, DC: US Government Printing Office.

Prince M. (1998). Measurement in psychiatry. *International Review of Psychiatry* 10: 264–271.

Radhakrishnan K, Pandian JD, Santoshkumar T, Thomas SV, Deetha TD, Sarma PS, Jayachandran D, Mohamed E. (2000). Prevalence, knowledge, attitude and practice of epilepsy in Kerala, South India. *Epilepsia* 41(8): 1027–1035.

Ramaratnam S, Baker GA, Goldstein L. (2001). Psychological treatments for epilepsy (Cochrane Review). *Cochrane Database Syst Rev* 4: CD002029.

Rapp SR, Parisi SA, Walsh DA. (1988). Psychological dysfunction and physical health among elderly medical in-patients. *J Consult Clin Psychol* 56: 851–855.

Redhead K. (2003). Perspectives from a developed nation. *Epilepsia* 44(Suppl. 1): 51–54.

Regier DA, Kaelber CT. (1995). The Epidemiologic Catchment Area (ECA) Program: studying the prevalence and incidence of psychopathology. In: Tsuang MT, Tohen M, Zahner GEP eds. *Textbook of Psychiatric Epidemiology*. New York: Wiley-Liss, pp. 135–156.

Reid AH. (1983). Psychiatry of mental handicap: a review. *J Roy Soc Med* 76: 587–592.

Reisberg B, Borenstein J, Salob SP, Ferris SH, Franssen E, Georgotas A (1987). Behavioral Symptoms in Alzheimer's Disease: Phenomenology and Treatment. *J Clin Psychiatry* 48 Suppl: 9-15.

Ridsdale L. (1995). Matching the needs with skills in epilepsy care. *British Medical Journal* 310: 1219–1220.

Ridsdale L, Robins D, Cryer C, Williams H. (1997). Feasibility and effects of nurse run clinics for patients with epilepsy in general practice; randomised controlled trial. *British Medical Journal* 314: 120–122.

Ridsdale L, Kwan I, Cryer C. (1999). The effect of a special nurse on patients' knowledge of epilepsy and their emotional state. Epilepsy Evaluation Care Group. *Br J Gen Pract* 49: 285–289.

Ridsdale L, Kwan I, Cryer C. (2000). Newly diagnosed epilepsy: can nurse specialists help? A randomised controlled trial. Epilepsy Care Evaluation Group. *Epilepsia* 41(8): 1014–1019.

Robins LN, Helzer JE, Croughan J, Ratcliff KS (1981). The NIMH Diagnostic Interview Schedule, its history, characteristics, and validity: *Arch Gen Psychiatry* 38:381-89.

Ross EM, Peckham CS. (1983). School children with epilepsy. In: Parsonage M, Grant RHE, Craig AG, eds. *Advances in Epileptology: XIV Epilepsy International Symposium*. New York: Raven Press, pp. 213–220.

Roy A. (1979). Some determinants of affective symptoms in epileptics. *Can J Psychiatry* 24: 554–556.

Rutter M, Graham P, Yule W. (1970). *A Neuropsychiatric Study in Childhood.* London: Heinemann Medical.

Sadock BJ, Sadock VA (2004). Kaplan and Sadock's Comprehensive Textbook of Psychiatry (CD-ROM for Windows & Macintosh. Single Seat Multi-User), Lippincott Williams & Wilkins.

Salazar AM, Jabbari B, Vance SC, Grafman J, Amin D, Dillon JD. (1985). Epilepsy after penetrating head injury. I. Clinical correlates: a report of the Vietnam Head Injury Study. *Neurology* 35: 1406–1414.

Salkind M. (1976). The assessment of drugs in general practice. *British Journal of Clinical Pharmacology* 3(Suppl.1): 69–72.

Samt P. (1875). Epileptische Irreseinsformen. *Arch Psychiatr* 5: 393–444 (Cited in Schmitz, 1998).

Samt P. (1876). Epileptische Irreseinsformen. *Arch Psychiatr* 6: 110–216 (Cited in Schmitz, 1998).

Sander JWAS, Shorvon SD. (1987). Incidence and prevalence studies in epilepsy and their methodological problems: a review. *J Neurol Neurosurg Psychiat* 50: 829–839.

Sander JW. (1993). Some aspects of prognosis in the epilepsies: a review. *Epilepsia* 34: 1007–1016.

Sander JW. (1995). The prognosis, morbidity and mortality of epilepsy. In: Duncan JS, Fish DR, Shorvon SD, eds. *Clinical Epilepsy*. Edinburgh: Churchill Livingstone, pp. 300–320.

Sander JW, Shorvon SD. (1996). The epidemiology of the epilepsies. *J Neurol Neurosurg Psychiat* 61: 433–443.

Sander JW, Sillanpaa. (1998). Natural history and prognosis. In: Engel J, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook.* Philadelphia: Lippincott-Raven, pp. 69–85.

Sander JW. (2002). The mortality of epilepsy. In: Duncan JS, Sidodiya SM, Smalls JE, eds. *Epilepsy 2002: From Science to Patient*, Lecture Notes. London: International League Against Epilepsy.

Sander JW, Shorvon SD. (2002). The incidence and prevalence of epilepsy. In: Duncan JS, Sidodiya SM, Smalls JE, eds. *Epilepsy 2002: From Science to Patient*, Lecture Notes. London: International League Against Epilepsy, pp. 1–6.

Sander JW (2003). Natural History of Untreated Epilepsy. *Epilepsia*, vol 44 (Suppl. 1).

Satishchandra P, Trimble MR. (2001). On being seizure-free. *Epilepsy Behav* 2: 4–7.

Savage G. (1892). Epilepsy and insanity. In: Duke DH, ed. *A Dictionary of Psychological Medicine*. Vol. 1. London: Churchill, pp. 452–454.

Schachter SC, Wheless JW. (2002). The evolving place of vagus nerve stimulation therapy. *Neurology* 59(6, Suppl.4): S1–S2.

Schmitz B, Trimble MR. (1992). Epileptic equivalents in psychiatry: some 19th century views. *Acta Neurol Scand* 86(Suppl. 140): 122–126.

Schmitz B. (1998). Forced normalization: history of a concept. In: Trimble MR, Schmitz B, eds. *Forced Normalization and Alternative Psychoses of Epilepsy.* Petersfield: Wrightson pp. 7–24.

Secretary of State for Health (1992). *The Health of the Nation: A Strategy for Health in England.* London: HMSO.

Senatore V, Matson JL, Kazdin AE. (1985). An inventory to assess psychopathology of mentally retarded adults. *Am J Ment Defic* 89(5): 459–466.

Shetty T, Trimble MR. (1997). The Bear Fedio inventory: twenty years on. *J Epilepsy* 10: 254–262.

Shorvon SD. (1982). The drug treatment of epilepsy: towards more effective anticonvulsant assessment and therapeutics. MD thesis. University of Cambridge (Cited in Sander & Shorvon, 1987).

Siegel RE. (1973). Gylen on psychology, psychopathology, and function and diseases of the nervous system. Karger: Basel.

Sillanpaa M. (1996). Epilepsy in the mentally retarded. In: Wallace S, ed. *Epilepsy in Children.* London: Chapman and Hall, pp. 417–427.

Sillanpaa M, Gram L, Johannessen SI, Tomson T, eds. (1999). *Epilepsy and Mental Retardation.* Petersfield: Wrightson Biomed.

Simon B. (1978). *Mind and Madness in Ancient Greece.* Ithaca: Cornell University Press.

Sisodiya SM. (2002). Syncope. In: Duncan JS, Sidodiya SM, Smalls JE, eds. *Epilepsy 2002: From Science to Patient*, Lecture Notes. London: International League Against Epilepsy, pp. 157–160.

Slater E, Beard AW. (1963). The schizophrenia-like psychoses of epilepsy. *Brit J Psychiat* 109: 95–150.

Smith DB, Craft BR, Collins J, Mattson RH, Cramer JA, and the VA Co-operative Study Group 118 (1986). Behavioural characteristics of epilepsy patients compared with normal controls. *Epilepsia* 27(6): 760–768.

Smith DF, Baker GA, Dewey M, Jacoby A, Chadwick DW. (1991). Seizure frequency, patient-perceived seizure severity and the psychosocial consequences of intractable epilepsy. *Epilepsy Res* 9(3): 231–241.

Spina E, Perucca E. (2002). Clinical significance of pharmacokinetic interactions between antiepileptic and psychotropic drugs. *Epilepsia* 43(Suppl. 2): 37–44.

Spitzer RL. (1983). Psychiatric diagnoses: are clinicians still necessary? *Compr Psychiatry* 24: 399–411.

Spitzer RL, Wakefield JC. (1999). DSM-IV diagnostic criterion for clinical significance: does it help solve the false positives problem? *Am J Psych* 156: 1856–1864.

Standage KF, Fenton, GW. (1975). Psychiatric symptom profiles of patients with epilepsy: a controlled investigation. *Psychol Med* 5: 152–160.

Stefansson SB, Olafsson E, Hauser AW. (1998). Psychiatric morbidity in epilepsy: a case controlled study of adults receiving disability benefits. *J Neurol Neurosurg Psychiatry* 64: 238–241.

Steffenberg U, Hagberg G, Kyllerman M. (1995). Active epilepsy in mentally retarded children. *Acta Paediatr Scand* 84: 1153–1159.

Steffenberg S, Gilberg C, Steffenberg U. (1996). Psychiatric disorders in children and adolescents with mental retardation and active epilepsy. *Arch Neurol* 53: 904–912.

Steffenberg E, Steffenberg S. (1999). Epilepsy and other neuropsychiatric morbidity in mentally retarded children. In: Sillanpaa M, Gram L, Johannessen S, I, Tomson T, eds. *Epilepsy and Mental Retardation.* Wrightson Biomed: Petersfield, pp. 47–59.

Stewart R (2003). Inference. In: Prince MJ, Stewart R, Ford T, Hotopf M (Eds.). *Practical Psychiatric Epidemiology*, Oxford, Oxford University Press.

Strickland BB, ed. (2000). *Gale Encyclopedia of Psychology.* II edn. Gale Group.

Swets JA, Harris JR, McElroy LS, Rudloe H (1964). Further Experiments on Computer-Aided Learning of Sound Identification. *Tech. Rep. Navtradevcen* 789-2. (cited in Thompson C, ed. *The Instruments of Psychiatric Research.* Chichester: John Wiley & Sons).

Swinkels WAM, Shackleton DP, Kasteleijn-Nolst Trenite, DGA. (2000). Psychosocial Impact of Epileptic Seizures in a Dutch Epilepsy Population: A Comparative Washington Psychosocial Seizure Inventory Study. *Epilepsia 2000* 41(10): 1335–1341.

Tabachnick BG, Fidell LS. (2000). *Understanding Multivariate Statistics.* 4th edn. Allyn & Bacon.

Taylor M. (1994). Epilepsy care: a need for change (editorial). *Br J Gen Pract* 44: 386–387.

Taylor M, Readman S, Hague B, Boulter V, Hughes L, Howell S. (1994). A district epilepsy service, with community-based specialist liaison nurses and guidelines for shared care. *Seizure* 3: 121–127.

Teasdale JD, Segal ZV, Williams JM, Ridgeway VA, Soulsby JM, Lau MA. (2000). Prevention of relapse/recurrence in major depression by mindfulness-based cognitive behavioural therapy. *J Consult Clin Psychol* 68: 615–623.

Tellenbach H. (1961). Epilepsie als Anfallsleiden und als Psychose. Uber alternative Psychosen paranoider Pragung bei "forceiter Normalisierung" (Landolt) des Elektroencephallogramms Epileptischer. *Nervenarzt* 36: 190–202.

Tellenbach H. (1965). Epilepsiaals Anfallsleiden und Als Psychose. *Der Nervenartz* 36: 190–202.

Temkin O. (1971). *The Falling Sickness.* Baltimore: Johns Hopkins University Press.

Terris M. (1964). *Goldberger on Pellagra.* Baton Rouge, Louisiana: Louisiana State University Press.

Thompson C. (1989). Introduction. In: Thompson C, ed. *The Instruments of Psychiatric Research.* Chichester: John Wiley & Sons, pp. 1–18.

Tissot SA. (1770). Traite de l'epilepsie. Paris (Cited in Trimble, 1991).

Tohen M, Bromet E, Murphy JM, Tsuang MT. (2000). Psychiatric epidemiology. *Harv Rev Psychiatry* Sep 8(3): 111–125.

Torta R, Keller R. (1999). Behavioural, psychotic and anxiety disorders in epilepsy: etiology, clinical features and therapeutic implications. *Epilepsia* 40(Suppl. 10): S2–S20.

Trimble MR. (1991). *The Psychoses of Epilepsy.* New York: Raven Press.

Trimble MR. (1998). New antiepileptic drugs and psychopathology. *Neuropsychobiology* 38(3): 149–151.

Trimble MR. (2000). Cognitive and personality profiles in patients with juvenile myoclonic epilepsy. In: Schmitz B, Sander T, eds. *Juvenile Myoclonic Epilepsy – The Janz Syndrome.* Petersfield: Wrightson Biomedical, pp. 101–111.

Tsai L, Tsuang MT (1979). The Mini-Mental State Test and computerized tomography. *Am J Psychiatry* 136(4A): 436-8.

Tsuang MT, Dempsey GM. (1979). Long-term outcome of major psychoses, II: schizoaffective disorder compared with schizophrenia. affective disorders, and a surgical control group. *Arch Gen Psychiatry* 36: 1302–1304.

Tsuboi T. (1984). Epidemiology of febrile and afebrile convulsions in children in Japan. *Neurology* 34: 175–181.

Ustun TB, Goldberg D, Cooper J, Simon GE, Sartorius N. (1995). New classification of mental disorders with management guidelines for use in primary care: ICD-10 PHC chapter five. *British Journal of General Practice* 45: 211–215.

Ustun TB, Von Korff M. (1995). Primary mental health services: access and provision of care. In: Ustun TB, Sartorius N, eds. *Mental Illness in General Health Care: An International Study.* Chichester: John Wiley and Sons, pp. 347–360.

Ustun TB, Sartorius N (1995). Eds, *Mental Illness in General Health Care: An International Study.* Chichester: John Wiley and Sons.

Victoroff JI, Benson DF, Grafton ST, Engel J Jr, Maziotta JC. (1994). Depression in complex partial seizures. Electroencephalography and cerebral metabolic correlates. *Arch Neurol* 51: 155–163.

Watts AE. (1992). The natural history of untreated epilepsy in a rural community in Africa. *Epilepsia* 33: 464–468.

Whitman S, Hermann BP, Gordon AC. (1984). Psychopathology in epilepsy: how great is the risk? *Biol Psychiatry* 19(2): 213–236.

Williams P, Tarnoplosky A, Hand D. (1980). Case definition and case identification in psychiatric epidemiology: review and assessment. *Psychol Med* 10: 101–114.

Williams JW, Noel PH, Cordes JA, Ramirez G, Pignone M. (2002). Is this patient clinically depressed? *JAMA* 287(9): 1160–1170.

Wing JK, Cooper JE, Sartorius, N. (1974). The description and classification of psychiatric symptoms. *An Instruction Manual for the PSE and CATEGO System.* London: Cambridge University Press.

Wing J, Mann S, Leff J, Nixon J. (1978). The concept of a "case" in psychiatric population surveys. *Psychol Med* 8: 203–217.

Wing J, Bebbington P, Robins LN. (1981). *What is a Case?: The Problem of Definition in Psychiatric Community Surveys.* London: Grant McIntyre Medical and Scientific.

Wing L. (1993). The definition and prevalence of autism: a review. *Eur Child Adolesc Psychiatry* 2: 61–74.

Wing L. (1980). The MRC handicaps, behaviour and skills (HBS) schedule. In: Stromgren E, Dupont A, Nielsen JA, eds. Epidemiological research as basis for organisation in extramural psychiatry. *Acta Psychiatr Scand* 62: 241–247.

Woermann FG, Duncan JS. (2000). Structural changes from juvenile myoclonic epilepsy: evidence from quantitative MRI. In: Schmitz B, Sander T, eds. *Juvenile Myoclonic Epilepsy: The Janz Syndrome.* Petersfield: Wrightson Biomedical, pp. 83–89.

Wolf P, Trimble MR. (1985). Biological antagonism and epileptic psychoses. *Br J Psychiatry* 146: 272–276.

Wolf P. (1991). Acute behavioural symptomatology at disappearance of epileptiform eeg abnormality: paradoxical or "forced" normalization. In: Smith DB, Treiman DM, Trimble MR, eds. *Neurobehavioral Problems in Epilepsy, Advances in Neurology.* Vol. 55. New York: Raven Press, pp. 127–142.

World Health Organization (1967). Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death. Based on the recommendations of the Eighth Conference, Geneva, 1965.

World Health Organization (1992a). The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. World Health Organization, Geneva.

World Health Organisation (1992b). Schedules for Clinical Assessment in Neuropsychiatry (SCAN). Division of Mental Health, Geneva.

World Health Organization (1995). Schedule for Clinical Assessment in Neuropsychiatry (SCAN), version 2. WHO, Geneva.

Wright J, Pickard N, Whitfield A, Hakin N. (2000). A population based study of the prevalence, clinical characteristics and the effect of ethnicity on epilepsy. *Seizure* 9(5): 309–313.

Zielinski JJ. (1974). Epilepsy and mortality rate and causes of death. *Epilepsia* 15: 191–201.

Zigmond AS, Snaith RP. (1983). The hospital anxiety and depression scale. *Acta Psychiatr Scand* 67: 361–370.

9. APPENDICES

9.1. MINI MENTAL STATE EXAMINATION

ITEM	PATIENT SCORE	NORMAL	COMMENTS
ORIENTATION			
Date		(1)	
Day		(1)	
Month		(1)	
Year		(1)	
Season		(1)	
Country		(1)	
County		(1)	
City		(1)	
Hospital		(1)	
Floor		(1)	
REGISTRATION			
Apple, Table, Penny		(3)	
No of trials			
ATTENTION/CALCULATION			
Serial 7's backwards (93,86,79,72,65)		(5)	
'World' backwards (dlrow)			
RECALL			
Apple		(1)	

Table		(1)	
Penny		(1)	
LANGUAGE			
Name pencil & watch		(2)	
Repeat sentence : NO IFS ANDS OR BUTS"			
Follow 3 stage command: Take paper in right hand, fold, put on table		(3)	
Read and obey the command		(1)	
Write a sentence of your choice		(1)	
Copy the design		(1)	

9.2. NATIONAL HOSPITAL SEIZURE SEVERITY SCALE

1. Record the name of the seizure types that occur under headings:	Type 1	Type 2	Type 3
SINCE THE LAST VISIT:			
2. Does the patient have a generalised convulsion during this type of seizure?			
Yes	4	4	4
No	0	0	0
3. How often has the patient fallen to the ground in this type of seizure?			
Nearly always or always:	4	4	4
Often	3	3	3
Occasionally	2	2	2
Never	0	0	0
4. Has this type of seizure caused any of the following? (score only the worst)			
Burns, scalds, deep cuts, fractures	4	4	4
Bitten tongue, severe headaches	3	3	3
Milder injuries or headaches	2	2	2
No injuries	0	0	0
5. How often has the patient been incontinent of urine in this type of seizure?			
Nearly always or always:	4	4	4

Often	3	3	3
Occasionally	2	2	2
Never	0	0	0
6. If the seizure causes loss of consciousness, is there a warning long enough for the patient to protect himself/herself? (no loss of consciousness/seizures only while asleep 0)			
Never	2	2	2
Sometimes	1	1	1
Nearly always or always	0	0	0
7. How long is it until the patient is really back to normal after the seizure?			
Less than 1 minute	0	0	0
Between 1 and 10m minutes	1	1	1
Between 10 minutes and 1 hour	2	2	2
Between 1 and 3 hours	3	3	3
More than 3 hours	4	4	4
8. Do the following events occur in this type of seizure?			
Seriously disruptive automatisms: shouting, wandering, undressing	4	4	4
Mild automatisms or focal jerking	2	2	2
None	0	0	0
Add 1 point to each column	1	1	1
Total score for each seizure type			

INSTRUCTIONS FOR COMPLETION: National Hospital Seizure Severity Scale (NHS3)

Define how many seizure types occur: e.g., aura, complex partial, generalised convulsion, and call these type 1,2,3 arbitrarily.

Apply questions 2–8 to each seizure type separately. As the NHS3 indicates current seizure severity, define the time frame: e.g., 1–3 months or time since last clinical visit. Use clinical judgement whether each factor occurs in the seizure type. Allow the patient to judge the frequency of the event. Then tick the box opposite the response options. The number in the box is the score for the question.

Q3: Only actual falls are recorded. If the seizures could cause falls but have not because they all occurred while in bed, then the score is 0.

Q7 refers to the time until the patient feels fully functional.

The column totals give the seizure severity score.

9.3. PSYCHOSIS SCREENING QUESTIONAIRE

In this health survey we have to ask about a whole range of experiences. Some of these experiences are quite rare. However, I would be very obliged if you would bear with us and answer the questions I am going to ask you now.

Q1. Over the past year, have there been times when you felt very happy indeed without a break for days on end?

Yes.....1----------(a)

Unsure.....2----------(Q2)

No.....3----------(Q2)

(a) Was there an obvious reason for this?

Yes.....1----------(Q2)

Unsure.....2----------(Q2)

No.....3----------(b)

(b) Did your friends or relatives think it was strange or complain about it?

Yes.....1----------Screen positive, end schedule.

Unsure.....2----------(Q2)

No.....3----------(Q2)

Q2. Over the past year, have you ever felt that your thoughts were directly interfered with or controlled by some outside force or person?

Yes.....1----------(a)

Unsure.....2---------(Q3)

No.....3--------(Q3)

(a) Did this come about in a way that many people would find hard to believe, for instance, through telepathy?

Yes.....1---------- Screen positive, End schedule.

Unsure.....2----------(Q3)

No.....3----------(Q3)

Q3. Over the past year have there been times when you felt that people were against you?

Yes.....1----------(a)

Unsure.....2----------(Q4)

No.....3----------(Q4)

(a) Have there been times when you felt that people were acting deliberately to harm you or your interests?

Yes.....1----------(b)

Unsure.....2----------(Q4)

No.....3----------(Q4)

(b) Have there been times when you felt that a group of people was plotting to cause you serious harm or injury?

Yes.....1----------Screen positive, End Schedule

Unsure.....2----------(Q4)

No.....3----------(Q4)

Q4. Over the past year, have there been times when you felt that something strange was going on?

Yes.....1----------(a)

Unsure.....2----------(Q5)

No.....3----------(Q5)

(a) Did you feel it was so strange that other people would find it very hard to believe?

Yes.....1----------Screen positive, End Schedule.

Unsure.....2----------(Q5)

No.....3----------(Q5)

Q5. Over the past year have there been times when you heard or saw things that other people couldn't?

Yes.....1----------(a)

Unsure.....2----------End schedule

No.....3----------End schedule

(a) Did you at any time hear voices saying quite a few words or sentences when there was no one around that might account for it?

Yes.....1----------Screen positive, End Schedule

Unsure.....2----------End Schedule

No.....3----------End Schedule

9.4. HOSPITAL ANXIETY AND DEPRESSION SCALE

NAME: _____ DATE: _____

Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings, he will be able to help you more. This questionnaire is designed to help your doctor to know how you feel. Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

TICK ONLY ONE IN EACH SECTION

I feel tense or 'wound up':

Most of the time [ ]

A lot of the time [ ]

Time to time, occasionally [ ]

Not at all [ ]

I still enjoy the things I used to enjoy:

Definitely as much [ ]

Not quite so much [ ]

Only a little [ ]

Hardly at all [ ]

I get a sort of frightened feeling as if something awful is about to happen:

Very definitely and quite badly [ ]

Yes, but not too badly [ ]

A little, but it doesn't worry me [ ]

Not at all [ ]

I can laugh and see the funny side of things:

As much as I always could [ ]

Not quite so much now [ ]

Definitely not so much now [ ]

Not at all [ ]

Worrying thoughts go through my mind:

A great deal of the time [ ]

A lot of the time [ ]

From time to time but not too often [ ]

Only occasionally [ ]

I feel as if I am slowed down:

Nearly all the time [ ]

Very often [ ]

Sometimes [ ]

Not at all [ ]

I get a sort of frightened feeling like 'butterflies' in the stomach:

Not at all

Occasionally

Quite often

Very often

I have lost interest in my appearance:

Definitely

I don't take as much care as I should

I may not take as much care

I take just as much care as ever

I feel restless as if I have to be on the move:

Very much indeed

Quite a lot

Not very much

Not at all

I look forward with enjoyment to things:

As much as ever I did

Rather less than I used to

Definitely less than I used to

Hardly at all

I feel cheerful:

Not at all

Not often

Sometimes

Most of the time

I can sit at ease and feel relaxed:

Definitely

Usually

Not often

Not at all

I get sudden feelings of panic:

Very often indeed

Quite often

Not very often

Not at all

I can enjoy a good book or radio or T.V. programme:

Often

Sometimes

Not often

Very seldom

9.5. Neurobehavioural Inventory

9.5.1. Introduction

On the following pages there are statements of personal attitudes and opinions. For each statement, please indicate whether the statement seems true or false from your point of view.

Simply place a check (√), under the appropriate column for each item, leaving no blanks. There are no right or wrong answers to this inventory, and what is most important is the honesty of your answers.

9.5.2. Patient Identification

NAME:_____SEX:

AGE:

Highest grade you completed in school

Occupation:

Hand used for writing:

If left handed, are you the only one in the family?

Age when seizures started:

Number of seizures on the average per month:

Are you: Married ( ) Divorced ( ) Separated( ) Single( ).

With whom do you live: Alone ( ) Spouse( ) Parents( ) Other:

Do you live in: the Country ( ) Small town ( ) City ( ).

Have you been in trouble with the police? If so, what kind?_____

Have you had a problem with alcohol?

Have you been addicted to drugs? _____If so, which ones?_____

Have you attempted suicide? _____.Have you been in a psychiatric hospital?_____If so, how many times?_____.Have you had psychiatric treatment?_____If so, what type?_____.

Date:_____.

9.5.3. Personal Inventory

		True	False
1.	I think people would learn a lot from the story of my life.	( )	( )
2.	I have at times feelings of blissful joy	( )	( )
3.	I feel like a pawn in the hands of others	( )	( )
4.	I can never forgive myself for some of the things that I have done	( )	( )
5.	I have a habit of counting things or memorising numbers	( )	( )
6.	It makes good sense to keep a detailed diary	( )	( )
7.	Sex is less important that most people believe	( )	( )
8.	I frequently have trouble getting a good night's sleep	( )	( )
9.	For me, feelings may suddenly take the place of thinking	( )	( )
10.	I am hardly ever preoccupied with thoughts about sex	( )	( )
11.	I believe that I serve a supreme purpose in life	( )	( )
12.	Fate appears to be working against me.	( )	( )

		True	False
13.	My religious beliefs have become very important	( )	( )
14.	I am more sensitive to distractions than other people	( )	( )
15.	I have gotten people angry by asking them to do so much for me	( )	( )
16.	I am very worried about hurting other people's feelings	( )	( )
17.	I am open to attack from many sides	( )	( )
18.	I write poetry, stories or biographies	( )	( )
19.	It makes me personally furious to see people disobeying the law	( )	( )
20.	Little things make me angrier than they used to	( )	( )
21.	If things are not just right, it upsets me	( )	( )
22.	People tend to take advantage of me	( )	( )
23.	Almost everything triggers some emotional reaction in me	( )	( )
24.	The Bible has a special meaning which I am beginning to understand	( )	( )
25.	My temper has gotten me into trouble	( )	( )
26.	Sometimes I get terribly confused by little details	( )	( )
27.	Powerful forces are acting through me	( )	( )
28.	I seem to depend on other people for many things	( )	( )
29.	Few things are really funny	( )	( )
30.	I am often bothered by severe headaches or other troublesome aches and pains	( )	( )
31.	Often, I get into such a good mood that I do foolish things	( )	( )
32.	I am sure there is a significant meaning behind my suffering	( )	( )
33.	I have had periods of days or weeks when I could not get going at all	( )	( )
34.	Sometimes I hear sounds or see things that are really not there	( )	( )
35.	I cannot get off the point sometimes	( )	( )

		True	False
36.	I am losing control of my temper more frequently	( )	( )
37.	Nothing is more important than trying to understand the forces that govern this world	( )	( )
38.	Life is a strain for me much of the time	( )	( )
39.	Sometimes I feel so helpless that I want people to do everything for me	( )	( )
40.	I may become fearful of being alone	( )	( )
41.	Often I am the only one to stand up for what is right	( )	( )
42.	Sometimes my mind gets stuck on so many different ideas that I cannot make a decision of do anything.	( )	( )
43.	When I get angry, I often explode	( )	( )
44.	Sometimes my mind gets stuck on one idea so that I cannot make a decision or do anything	( )	( )
45.	People do not seem to appreciate my jokes	( )	( )
46.	I spend a lot of time thinking of the origins of the world and life itself	( )	( )
47.	I suffer from frequent periods of exhaustion or fatigue	( )	( )
48.	I have had some very intense religious experiences	( )	( )
49.	Almost everyday I am infuriated by cases where justice has not been done	( )	( )
50.	It is useless to tell people something without giving them all the details	( )	( )
51.	Powerful forces outside my control are working with my life	( )	( )
52.	My sexual activity has decreased	( )	( )
53.	I write down or copy many things	( )	( )
54.	Emotions control my life	( )	( )
55.	Much of the time I feel as if I have done something wrong or harmful	( )	( )
56.	I have a tendency to break things or hurt people when I get infuriated	( )	( )

		True	False
57.	I often feel suddenly fearful without apparent reason	( )	( )
58.	Before I make a decision, I need to know every detail	( )	( )
59.	Sometimes I feel so good that ideas come faster into my mind than I can handle them	( )	( )
60.	Once I start to talk to someone, I have trouble breaking off	( )	( )
61.	I have not lived the right kind of life	( )	( )
62.	I record special details of my life and thinking.	( )	( )
63.	At times I believe in something that in fact is not taking place	( )	( )
64.	I tend to avoid crowds	( )	( )
65.	I have had periods when I was so full of pep that sleep did not seem necessary for several days	( )	( )
66.	People should think more carefully about the point of many jokes instead of just laughing at them	( )	( )
67.	I need more details than most people do before I understand something	( )	( )
68.	My feelings of hatred can be very intense	( )	( )
69.	I am subject to big shifts in mood	( )	( )
70.	When I accidentally hurt someone's feelings, I cannot forgive myself for a long time	( )	( )
71.	I tend to get bogged down with the fine points of a situation	( )	( )
72.	Finally I am beginning to understand the real meaning or nature of this world	( )	( )
73.	I really am down in the dumps most of the time	( )	( )
74.	I worry often about my physical health	( )	( )
75.	I would go out of my way to make sure that the law is followed	( )	( )

		True	False
76.	I have more of a feeling than most people for the order and purpose of life	( )	( )
77.	I can do easily without sexual activity	( )	( )
78.	Sometimes I keep at a thing for so long that others may lose their patience with me	( )	( )
79.	Sometimes without any reason or even when things are going wrong I feel excitedly happy, on top of the world	( )	( )
80.	I really make myself suffer after even a small mistake	( )	( )
81.	People sometimes tell me that I have trouble getting to the point because of all the details	( )	( )
82.	I would like to rip some people to shreds	( )	( )
83.	I detest people who try to break the rules	( )	( )
84.	I have trouble becoming sexually aroused	( )	( )
85.	I have often felt so bad that I was close to ending my life	( )	( )
86.	I am more afraid of doing the wrong thing than most people	( )	( )
87.	The thought of revenge burns inside me	( )	( )
88.	Most jokes do not seem funny to me	( )	( )
89.	My emotions have been so powerful that they have caused trouble	( )	( )
90.	Sometimes a particular thought will run through my head and bother me for days	( )	( )
91.	I am often said to be hot-headed	( )	( )
92.	The future may suddenly seem hopeless to me	( )	( )
93.	I am fortunate to receive so much help from people around me	( )	( )
94.	I am very religious (more than most people) in my own way	( )	( )
95.	I am bothered off and on by odd physical sensations	( )	( )

		True	False
96.	When I think of some of the things that people have done to me, it makes me absolutely furious	( )	( )
97.	Sometimes I think an illness has been given to me so that I would meet certain people at the right time	( )	( )
98.	I would like to write a book	( )	( )
99.	Religion and God are more personal experiences for me than most people	( )	( )
100.	There is too much foolishness in the world these days	( )	( )

Thank you for your honest and patient completion of the survey. Would you please check to be sure that all the questions were answered.

9.5.4. Personal Behaviour Inventory

(Carer Version)

Instructions

On the following pages are statements about personal habits, preferences, feelings and beliefs. For each statement, please indicate if the statement seems more true of false about the person you are describing. On the basis of your experiences with the patient, please give your first and most honest response to each item, leaving no blanks. There are no right or wrong answers – no rating of better or worse, so please be guided by your memory and your impressions.

We appreciate your sincere co-operation in completing the survey.

PLEASE FILL IN:

1.----------

Name of the person you are describing

2.----------

Your name

3.----------

Your relation to the patient

4.----------

Your sex

5.----------

Your age

6.----------

Highest grade you completed at school

7.----------

Number of years you have known the patient

8----------

Date

		True	False
(A)	Writing Tendency	( )	( )
1.	Believes it would be good sense to keep a detailed diary	( )	( )
2	Writes poetry, stories or biography	( )	( )
3.	Writes down many things, copies passages from books, and so forth	( )	( )

4.	Records details about personal experiences and thinking	( )	( )
5.	Speaks about or is writing a book		
(B)	Sense of law and order	( )	( )
6.	Personally very upset when people disobey the law	( )	( )
7.	Often believes that he or she is the only person who is right	( )	( )
8.	Infuriated by cases where justice is not done	( )	( )
9.	Goes out of the way to make sure the law is followed	( )	( )
10.	Detests people who break the law	( )	( )
(C)	Religious Convictions		
11.	Religious beliefs have become very important	( )	( )
12.	Believes that the Bible has special meaning that he or she can understand	( )	( )
13.	Has had some very intense religious experiences	( )	( )
14.	Very religious (more that most people) in own way	( )	( )
15.	Religion and God are more personal experiences for him/her than most people		
(D)	Anger and Temper		
16.	Little things make him or her more angry than they used to	( )	( )
17.	Gets into trouble because of temper	( )	( )
18.	Loses control of temper more frequently	( )	( )
19.	When angry, often explodes	( )	( )
20.	Often said to be hot-headed	( )	( )
(E)	Orderliness		
21.	Has a habit of counting things or memorising numbers	( )	( )
22.	Seems more sensitive to distractions than most people	( )	( )
23.	Becomes upset if things are not just right	( )	( )

24.	Mind gets stuck on so many ideas that he or she cannot make a decision about anything	( )	( )
25.	Tends to get bogged down with the fine points of the situation	( )	( )
(F)	Feelings About Sex	True	False
26.	Sex is less important than most people believe	( )	( )
27.	Hardly ever preoccupied with thoughts about sex	( )	( )
28.	Sexual activity has decreased	( )	( )
29.	Can do easily without sexual activity	( )	( )
30.	Has trouble becoming sexually aroused	( )	( )
(G)	Fearfulness		
31.	Is very worried about hurting other people's feelings	( )	( )
32.	May become fearful of being alone	( )	( )
33.	Often becomes fearful without apparent reason	( )	( )
34.	Tends to avoid crowds	( )	( )
35.	Is more afraid of doing the wrong thing than most people	( )	( )
(H)	Feelings of Guilt		
36.	Can never forgive himself for some of the things he has done	( )	( )
37.	Much of the time feels as if he or she has done something wrong or harmful	( )	( )
38.	Believes he or she has not lived the right kind of life	( )	( )
39.	After accidentally hurting someone's feelings cannot forgive himself or herself for a long time	( )	( )
40.	Really suffers even after a small mistake	( )	( )
(I)	Seriousness		
41.	Finds few things really funny	( )	( )

42.	People do not seem to appreciate his or her jokes	( )	( )
43.	Feels that people should think about the point of many jokes carefully instead of just laughing at them	( )	( )
44.	Feels that most jokes are not funny	( )	( )
45.	Says there is too much foolishness in the world these days	( )	( )
(J)	Sadness		
46.	Has had periods of days or weeks when he or she could not get going at all	( )	( )
47.	Feels that life is a strain much of the time	( )	( )
48.	Really down in the dumps most of the time	( )	( )
49.	Has often felt close to ending his or her life	( )	( )
50.	May feel suddenly that the future is hopeless	( )	( )
(K)	Emotions	True	False
51.	Feelings may suddenly take the place of thinking	( )	( )
52.	Almost everything triggers some emotional reaction	( )	( )
53.	Emotions control his or her life	( )	( )
54.	Subject to big shifts of mood	( )	( )
55.	Emotions have been so powerful that they have caused trouble	( )	( )
(L)	Suspicion		
56.	Feels that fate is working against him/her	( )	( )
57.	Open to attack from many sides	( )	( )
58.	Believes that people tend to take advantage of him or her	( )	( )
59.	Sometimes may see things or hear sounds which are not really there	( )	( )
60.	At times may believe in something that in fact is not taking place	( )	( )
(M)	Interest in Details		

61.	Sometimes gets terribly confused by little details	( )	( )
62.	Rarely tells people something without giving them all the details	( )	( )
63.	Needs to know every detail before making a decision	( )	( )
64.	Needs more details than most people to understand something	( )	( )
65.	Has trouble getting to the point because of all the details	( )	( )
(N)	Cosmic Interests		
66.	Believes that nothing is more important than trying to understand the forces that govern this world	( )	( )
67.	Spends a lot of time thinking about the origins of the world and life	( )	( )
68.	Believes that powerful forces beyond control are working with his or her life	( )	( )
69.	Believes he or she understands the real meaning or nature of this world	( )	( )
70.	More preoccupied than most people with the order and purpose of life	( )	( )
(O)	Sense of personal Destiny		
71.	Feels people would learn a lot from the story of his or her life	( )	( )
72.	Thinks that he or she serves a supreme purpose in life	( )	( )
73.	Believes that powerful forces are acting through him or her	( )	( )
74.	Seems sure there is a significant meaning behind personal suffering	( )	( )
75.	Feels that the illness has been given so that she or he would meet certain people at the right time	( )	( )
(P)	Persistence and Repetitiveness	True	False
76.	Cannot get off the point sometimes	( )	( )
77.	Sometimes gets stuck on one idea so that he or she cannot make a decision or do anything	( )	( )
78.	When talking to someone has trouble breaking off	( )	( )

79.	Sometimes keeps at a thing so long that others may lose their patience	( )	( )
80.	Is bothered for days by the same thoughts	( )	( )
(Q)	Hatred and Revenge		
81.	Has a tendency to break things or hurt people when infuriated	( )	( )
82.	Feelings of hatred can be very intense	( )	( )
83.	Talks about ripping some people to shreds	( )	( )
84.	Preoccupied by thoughts of revenge	( )	( )
85.	Infuriated by some of the things people have done to him or her	( )	( )
(R)	Dependency		
86.	Feels like a pawn in the hands of others	( )	( )
87.	Has gotten people angry by asking them to do so much	( )	( )
88.	Seems to depend on other people for many things.	( )	( )
89.	Sometimes feels so helpless that he wants other people to do everything	( )	( )
90.	Feels fortunate to receive so much help from people	( )	( )
(S)	Happiness		
91.	Has at times feelings of intense joy	( )	( )
92.	Often does foolish things while in a good mood	( )	( )
93.	Sometimes feels so good that ideas come into mind faster that he or she can handle them	( )	( )
94.	Has periods full of pep that sleep did not seem necessary for several days	( )	( )
95.	Sometimes feels excitedly happy, on top of the world, without any reason or even when things are going wrong	( )	( )
(T)	Physical Well-Being		
96.	Frequently has trouble getting a good night's sleep	( )	( )
97.	Is often bothered by severe headaches or other troublesome aches and	( )	( )

pains

98.	Suffers from frequent periods of exhaustion or fatigue	( )	( )
99.	Worries about his or her physical health	( )	( )
100.	Is bothered by various odd bodily sensations off and on	( )	( )

9.6. Neuropsychiatric Inventory

General Instructions

• Mark 'YES' or 'NO' for whether the behaviour is present or not, or if the question is not applicable (screening question).

• Mark all boxes for which the answer to the corresponding question is 'YES'.

• Give a score for the frequency of the behaviour (1–4) and for the severity of the behaviour (1–3)

• Give a score for the distress of the caregiver (0–5).

• Calculate the total score as frequency x severity.

Instructions for administration of NPI

• The interview is best conducted with the caregiver in the absence of the patient to facilitate an open discussion of behaviours that may be difficult to describe with the patient present. Information may be augmented by direct observation and questioning of the patient.

Questions should be asked exactly as written. Clarifications should be provided if the caregiver does not understand the question.

Acceptable clarifications are restatements of the questions in alternate terms. The answers pertain to changes in the patient's behaviour that have appeared since the onset of the illness. Behaviours that have been present throughout the patient's life and have not changed in the course of the illness are not scored even if they are abnormal (e.g., anxiety, depression). Behaviours that have been present throughout life but have changed since the illness are scored (e.g., the patient has always been apathetic but there has been a notable increase in apathy during the period of inquiry).

Remind the respondent periodically that the answers pertain to changes in the patient's behaviour that have appeared since the onset of the illness.

• The NPI may be used to address changes occurring in response to treatment or that have changed since the last clinic visit. The time frame of the question would than be revised to reflect this interest in recent changes. Emphasize to the caregiver that the questions pertain to behaviours that have appeared or changed since the onset of the illness. For e.g., the questions might be phrased "Since he/she began treatment with the new medications..." or "Since the dosage of ____ was increased.....".

• The screening question is asked to determine if the behavioural change is present or absent. If the answer to the screening question is negative, mark NO and proceed to the next screening question without asking the sub-questions. If the answer to the screening question is positive or if there are any uncertainties in the caregiver's response or any inconsistencies between the response and other information known by the clinician (e.g., the caregiver responds negatively to the euphoria screening question but the patient appears euphoric to the clinician).The category is explored in more depth with the sub-questions.

• If the sub-questions confirm the screening question, the severity and frequency of the behaviour are determined according to the criteria provided with each behaviour. When determining frequency and severity use the behaviours identified by the sub-questions as most aberrant. For example, if the caregiver indicates that resistive behaviour is particularly problematic when you are asking the sub-questions of the agitation section, then use resistive behaviour to prompt judgements regarding the frequency and severity of agitation. If two behaviours are very problematic, use the frequency and severity of both behaviours to score the item. For e.g., if the patient has

two types or more of delusions, then use the severity of the most severe and the frequency of any delusional behaviours.

• In some cases, the caregiver will provide a positive response to the screening question and a negative reply to all sub-questions. If this happens, ask the caregiver to expand on why they responded affirmatively to the screen. If they provide information relevant to the behavioural domain but in different terms, the behaviour should be scored for severity and frequency as usual. If the original affirmative response was erroneous, leading to a failure to endorse any sub-questions, then the behaviour is rescored as absent ('NO' on the screen).

• Some sections such as the questions pertaining to appetite are framed so as to capture whether there is an increase or decrease in the behaviour (increased or decreased appetite or weight). If the caregiver answers 'yes' to the first member of the paired question (such as has the patient's weight decreased?), do not ask the second question (has the patient's weight increased?) since the answer to the second question is contained the in the answer to the first. If the caregiver answers 'no' to the first member of the pair of questions, then the second question must be asked.

• When determining frequency, say to the person being interviewed "Now I want to find out how often these things (define using the description of the behaviours they noted as most problematic on the sub-questions) occur. Would you say that they occur less than once per week, about once per week, several times per week but not every day, or every day?" Some behaviours, such as apathy, eventually become continuously present, and then 'are constantly present' can be substituted for 'every day'. When determining severity, tell the person being interviewed "Now I would like to find out how severe these behaviours are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that (the behaviours) are mild,

moderate or severe?" Additional descriptors are provided in each section that may be used to help the interviewer clarify each grade of severity. When beginning the inventory, say to the caregiver "These questions are designed to evaluate your (husband's/wife's/etc.) behaviour. They can usually be answered "yes" or "no" so please try to be brief in your responses". If the caregiver lapses into elaborate responses that provide little useful information, they may be reminded of the need to be brief. In each case, be sure that the caregiver provides you with a definite answer as to the frequency and severity of the behaviours. Do not guess what the caregiver would say based on your discussion.

• In very impaired patients or in patients with special medical circumstances, a set of questions may not be applicable. For e.g., bed-bound patients may exhibit hallucinations or agitation but could not exhibit aberrant motor behaviour. If the clinician or the caregiver believes that the questions are inappropriate, then the section should be marked not applicable, and no further data are recorded for that section. Likewise, if the clinician feels that the responses are invalid (e.g., the caregiver did not seem to understand the particular set of questions asked), not applicable should also be marked.

• When each domain is completed and the caregiver has completed the frequency and severity rating, you may want to ask the associated caregiver distress question. To do this, simply ask the caregiver how much, if any, "emotional or psychological" distress the behaviour he or she just discussed causes him or her (the caregiver).The caregiver must rate their own distress on a five point scale from 0 – no distress, 1 – minimal, 2 – mild, 3 – moderate, 4 – moderately severe, 5 – very severe or extreme.

9.6.1. Neuropsychiatric Inventory with Caregiver Distress Scale

Subject's initials

A. Delusions

Does the patient have beliefs that you know are not true? For example, insisting that people are trying to harm him/her or steal from him/her. Has he/she said the family members are not who they say they are or that the house is not their home? I'm not asking about mere suspiciousness, I am interested if the patient is convinced that these things are happening to him/her.

[ ] not applicable no (proceed to next screening question) [ ] yes (proceed to subquestions)

[ ] Does the patient believe that he/she is in danger – that others are planning to hurt him/her?

[ ] Does the patient believe that others are stealing from him/her?

[ ] Does the patient believe that his/her spouse is having an affair?

[ ] Does the patient believe that unwelcome guests are living in his/her house?

[ ] Does the patient believe that his/her spouse or others are not who they claim to be?

[ ] Does the patient believe that his/her house is not his/her home?

[ ] Does the patient believe that family members plan to abandon him/her?

[ ] Does the patient believe that television or magazine figures are actually present in the home? (does he/she try to talk or interact with them?)

[ ] Does the patient believe any other unusual things that I haven't asked about?

A-Frequency:

occasionally – less than once per week

often – about once per week

frequently – several times per week but less than every day

very frequently – once or more per day

B-Severity:

mild – delusions present but seem harmless and produce little distress in the patient

moderate – delusions are distressing and disruptive

marked – delusions are very disruptive and are a major source of behavioural disruption

(if PRN medications are prescribed, their use signals that the delusions are of marked severity)

C-Distress:

How emotionally distressing do you find this behaviour?

not at all

minimally

mildly

moderately

severely

very severely or extremely

Date of this examination

1 2 fam. day month year

Total Delusions (AxB)

Subject's initials

B. Hallucinations

Does the patient have hallucinations such as false visions or voices? Does he/she seem to see, hear or experience things that are not present? By this question we do not mean just mistaken beliefs such as stating that someone who has died is still alive, rather we are asking if the patient actually has abnormal experiences of sounds, or visions.

not applicable no (proceed to next screening question) yes (proceed to subquestions)

Does the patient describe hearing voices or act as if he/she hears voices?

Does the patient talk to people who are not there?

Does the patient describe seeing things not seen by others or behave as if he/she is seeing things not seen by others (people, animals, lights, etc.)?

Does the patient report smelling odours not smelled by others?

Does the patient describe feeling things on his/her skin or otherwise appear to be feeling things crawling or touching him/her?

Does the patient describe tastes that are without any known cause?

Does the patient describe any other unusual sensory experience?

A-Frequency:

occasionally – less than once per week

often – about once per week

frequently – several times per week but less than every day

very frequently – once or more per day

B-Severity:

[ ] **mild** – hallucinations present but seem harmless and cause little distress for the patient

[ ] **moderate** – hallucinations are distressing and are disruptive to the patient

[ ] **marked** – hallucinations are very disruptive and are a major source of behavioural disturbance.

(PRN medications may be required to control them).

C-Distress:

How emotionally distressing do you find this behaviour?

[ ] not at all

[ ] minimally

[ ] mildly

[ ] moderately

[ ] severely

[ ] very severely or extremely

Date of this examination

1 2 fam. day month year

Total Hallucinations (AxB)

Subject's initials

C. Agitation/Aggression

Does the patient have periods when he/she refuses to cooperate or won't let people help him/her? Is he/she hard to handle?

not applicable no (proceed to next screening question) yes (proceed to sub-questions)

Does the patient get upset with those trying to care for him/her or resist activities such as bathing or changing clothes?

Is the patient stubborn, having to have things his/her way?

Is the patient uncooperative, resistive to help from others?

Does the patient have any other behaviours that make him/her hard to handle?

Does the patient shout or curse angrily?

Does the patient slam doors, kick furniture, throw things?

Does the patient attempt to hurt or hit others?

Does the patient have any other aggressive or agitated behaviours?

A-Frequency:

occasionally – less than once per week

often – about once per week

frequently – several times per week but less than every day

very frequently – once or more per day

B-Severity:

mild – behaviour is disruptive but can be managed with redirection or reassurance

moderate – behaviours disruptive and difficult to redirect or control

[ ] marked – agitation is very disruptive and difficult to redirect or control; there may be a threat of personal harm. Medications are often required

C-Distress:

How emotionally distressing do you find this behaviour?

[ ] not at all

[ ] minimally

[ ] mildly

[ ] moderately

[ ] severely

[ ] very severely or extremely

Date of this examination

1 2 fam. day month year

Total Agitations/Aggression (AxB)

Subject's initials

D. Depression/Dysphoria

Does the patient seem sad or depressed? Does he/she say that he/she feels sad or depressed?

[ ] not applicable no (proceed to next screening question) [ ] yes (proceed to subquestions)

Does the patient have periods of tearfulness or sobbing that seem to indicate sadness?

[ ] Does the patient say or act as if he/she is sad or in low spirits?

[ ] Does the patient put him/herself down or say that he/she feels like a failure?

[ ] Does the patient say that he/she is a bad person or deserves to be punished?

[ ] Does the patient seem very discouraged or say that he/she has no future?

[ ] Does the patient say he/she is a burden to the family or that the family would be better off without him/her?

[ ] Does the patient express a wish for death or talk about killing him/herself?

[ ] Does the patient show any other signs of depression or sadness?

A-Frequency:

[ ] occasionally – less than once per week

[ ] often – about once per week

[ ] frequently – several times per week but less than every day

[ ] very frequently – essentially continuously present

B-Severity:

[ ] mild – depression is present but usually responds to redirection or reassurance

[ ] moderate – depression is distressing, depressive symptoms are spontaneously voiced by the patient and difficult to alleviate

[ ] marked – depression is very distressing and a major source of suffering for the patient

C-Distress:

How emotionally distressing do you find this behaviour?

not at all

minimally

mildly

moderately

severely

very severely or extremely

Date of this examination

1 2 fam. day month year

Total Depression/Dysphoria (AxB)

Subject's initials

E. Anxiety

Is the patient very nervous, worried or frightened for no apparent reason? Does he/she seem very tense or fidgety? Is the patient afraid to be apart from you?

not applicable ☐ no (☐ proceed to next screening question) ☐ yes (☐ proceed to subquestions)

Does the patient say that he/she is worried about planned events?

Does the patient have periods of feeling shaky, unable to relax, or feeling excessively tense?

Does the patient have periods of (or complain of) shortness of breath, gasping or sighing for no other reason other than nervousness?

Does the patient complain of butterflies in his/her stomach, or of racing or pounding of the heart in association with nervousness? (Symptoms not explained by ill health)

[ ] Does the patient avoid certain places or situations that make him/her more nervous such as riding in the car, meeting with friends, or being in crowds?

[ ] Does the patient become nervous and upset when separated from you (or his/her caregiver)? (does he/she cling to you to keep from being separated?)

[ ] Does the patient show any other signs of anxiety?

A-Frequency:

[ ] occasionally – less than once per week

[ ] often – about once per week

[ ] frequently – several times per week but less than every day

[ ] very frequently – once or more per day

B-Severity:

[ ] mild – anxiety is distressing but usually responds to redirection or reassurance

[ ] moderate – anxiety is distressing, anxiety symptoms are spontaneously voiced by the patient and difficult to alleviate

[ ] marked anxiety is very distressing and a major source of suffering for the patient

C-Distress:

How emotionally distressing do you find this behaviour?

[ ] not at all

[ ] minimally

mildly

moderately

severely

very severely or extremely

Date of this examination

1 2 fam. day month year

Total Anxiety (AxB)

Subject's initials

F. Elation/Euphoria

Does the patient seem to be too cheerful or too happy for no reason? I don't mean the normal happiness that comes from seeing friends, receiving presents, or spending time with family members. I am asking if the patient has a persistent and abnormally good mood or finds humour where others do not

[] not applicable [] no ([] proceed to next screening question) □ yes (□ proceed to subquestions)

[]. Does the patient appear to feel too good or to be too happy, different from his/her usual self?

[] Does the patient find humour and laugh at things that others do not find funny?

[] Does the patient seem to have a childish sense of humour with a tendency to giggle or laugh inappropriately (such as when unfortunate things happens to others)?

[] Does the patient tell jokes or make remarks that have little humour for others but seem funny to him/her?

Does he/she play childish pranks such as pinking or playing "keep away" for the fun of it?

Does the patient "talk big" or claim to have more abilities or wealth than is true?

Does the patient show any other signs of feeling too good or being too happy?

A-Frequency:

[ ] occasionally – less than once per week

[ ] often – about once per week

[ ] frequently – several times per week but less than every day

[ ] very frequently – essentially continuously present

B-Severity:

[ ] mild – elation is notable to friends and family but is not disruptive

[ ] moderate – elation is notably abnormal

[ ] marked – elation is very pronounced, patient is euphoric and finds nearly everything to be humourous

C-Distress:

How emotionally distressing do you find this behaviour?

[ ] not at all

[ ] minimally

[ ] mildly

[ ] moderately

[ ] severely

[ ] very severely or extremely

Date of this examination

1 2 fam. day month year

Total Elation/Euphoria (AxB)

Subject's initials

G. Apathy/Indifference

Has the patient lost interest in the world around him/her? Has he/she lost interest in doing things or lack motivation for starting new activities? Is he/she more difficult to engage in conversation or in doing chores? Is the patient apathetic or indifferent?

not applicable ☐ no (☐ proceed to next screening question) ☐ yes (☐ proceed to subquestions)

Does the patient seem less spontaneous and less active than usual?

Is the patient less likely to initiate a conversation?

Is the patient less affectionate or lacking in emotions when compared to his/her usual self?

Does the patient contribute less to household chores?

Does the patient seem less interested in the activities and plans of others?

Has the patient lost interest in friends and family members?

Is the patient less enthusiastic about his/her usual interests?

Does the patient show any other signs that she doesn't care about doing new things?

A-Frequency:

occasionally – less than once per week

often – about once per week

frequently – several times per week but less than every day

very frequently – nearly always present

B-Severity:

mild – apathy is notable but produces little interference with daily routines; only mildly different from patient's usual behaviour; patient responds to suggestion to engage in activities

moderate – apathy is very evident; may be overcome by the caregiver with coaxing and encouragement; responds spontaneously only to powerful events such as visits from close relatives or family members

marked – apathy is very evident and usually fails to respond to any encouragement or external events

C-Distress:

How emotionally distressing do you find this behaviour?

not at all

minimally

mildly

moderately

severely

very severely or extremely

Date of this examination

1 2 fam. day month year

Total Apathy/Indifference (AxB)

Subject's initials

H. Disinhibition

Does the patient seem to act impulsively without thinking? Does he/she do or say things that are not usually done or said in public? Does he/she do things that are embarrassing to you or others?

[ ] not applicable [ ] no (proceed to next screening question) [ ] yes ([ ] proceed to subquestions)

[ ] Does the patient act impulsively without appearing to consider the consequences?

[ ] Does the patient talk to total strangers as if he/she knew them?

[ ] Does the patient say things to people that are insensitive or hurt their feelings?

[ ] Does the patient say crude things or make sexual remarks that they would not usually have said?

[ ] Does the patient talk openly about very personal or private matters not usually discussed in public?

[ ] Does the patient take liberties or touch or hug others in a way that is out of character for him/her?

[ ] Does the patient show any other signs of loss of control of his/her impulses?

A-Frequency:

occasionally – less than once per week

often – about once per week

frequently – several times per week but less than every day

very frequently – essentially continuously present

B-Severity:

mild – disinhibition is notable but usually responds to redirection and guidance

moderate – disinhibition is very evident and difficult to overcome by the caregiver

marked – disinhibition usually fails to respond to any intervention by the caregiver, and is a source of embarrassment or social distress

C-Distress:

How emotionally distressing do you find this behaviour?

not at all

minimally

mildly

moderately

severely

very severely or extremely

Date of this examination

1 2 fam. day month year

Total Disinhibition (AxB)

Subject's initials

I. Irritability/Lability

Does the patient get irritated and easily disturbed? Are his/her moods very changeable? Is he/she abnormally impatient? We do not mean frustration over memory loss or inability to perform usual tasks; we are interested to know if the patient has abnormal irritability, impatience, or rapid emotional changes different from his/her usual self.

not applicable ☐ no (☐ proceed to next screening question) ☐ yes (☐ proceed to subquestions)

☐ Does the patient have a bad temper, flying "off the handle" easily over little things?

☐ Does the patient rapidly change moods from one to another, being fine one minute and angry the next?

☐ Does the patient have sudden flashes of anger?

☐ Is the patient impatient, having trouble coping with delays or waiting for planned activities?

☐ Is the patient cranky and irritable?

☐ Is the patient argumentative and difficult to get along with?

☐ Does the patient show any other signs of irritability?

A-Frequency:

occasionally – less than once per week

often – about once per week

frequently – several times per week but less than every day

very frequently – essentially continuously present

B-Severity:

mild – irritability or lability is notable but usually responds to redirection and reassurance

moderate – irritability and lability are very evident and difficult to overcome by the caregiver

marked – irritability and lability are very evident, they usually fail to respond to any intervention by the caregiver, and they are a major sources of distress

C-Distress:

How emotionally distressing do you find this behaviour?

not at all

minimally

mildly

moderately

severely

very severely or extremely

Date of this examination

1 2 fam. day month year

Total Irritability/Lability (AxB)

Subject's initials

J. Aberrant Motor Behaviour

Does the patient pace, do things over and over such as opening closets or drawers, or repeatedly pick at things or wind string or threads?

not applicable ☐ no (☐ proceed to next screening question) yes (☐ proceed to subquestions)

Does the patient pace around the house without any apparent purpose?

Does the patient rummage around opening and unpacking drawers or closets?

Does the patient repeatedly put on and take off clothing?

Does the patient have repetitive activities or "habits" that he/she performs over and over?

Does the patient engage in repetitive activities such as handling buttons, picking, wrapping string, etc.?

Does the patient fidget excessively, seem unable to sit still, or bounce his/her feet or tap his/her fingers a lot?

Does the patient do any other activities over and over?

A-Frequency:

occasionally – less than once per week

often – about once per week

frequently – several times per week but less than every day

very frequently – essentially continuously present

B-Severity:

mild - abnormal motor activity is notable but produces little interference with daily routines

moderate – abnormal motor activity is very evident; can be overcome by the caregiver

marked – abnormal motor activity is very evident, it usually fails to respond to any intervention by the caregiver and is a major source of distress

C-Distress:

How emotionally distressing do you find this behaviour?

not at all

minimally

mildly

moderately

severely

very severely or extremely

Date of this examination

1 2 fam. day month year

Total Aberrant motor behaviour (AxB)

Subject's initials

K. Sleep

Does the patient have difficulty sleeping (do not count as present if the patient simply gets up once or twice per night only to go to the bathroom and falls back asleep

immediately)? Is he/she up at night? Does he/she wander at night, get dressed or disturb your sleep?

not applicable ☐ no (☐ proceed to next screening question) ☐ yes (☐ proceed to subquestions)

Does the patient have difficulty falling asleep?

Does the patient get up during the night (do not count if the patient simply gets up once or twice per night only to go to the bathroom and falls back asleep immediately)?

Does the patient wander, pace or get involved in inappropriate activities at night?

Does the patient awaken you during the night?

Does the patient awaken during the night, dress and plan to go out, thinking that it is morning and time to start the day?

Does the patient awaken too early in the morning (earlier that was his/her habit)?

Does the patient sleep excessively during the day?

Does the patient have any other night-time behaviours that bother you that we haven't talked about?

A-Frequency:

occasionally – less than once per week

often – about once per week

frequently – several times per week but less than every day

very frequently – once or more per day

B-Severity:

[ ] mild – night-time behaviours occur but they are not particularly disruptive

[ ] moderate – night-time behaviours occur and disturb the patient and the sleep of the caregiver; more than one type of night-time behaviour may be present

[ ] marked – night-time behaviours occur; several types of night-time behaviour may be present; the patient is very distressed during the night and the caregiver's sleep is markedly disturbed

C-Distress:

How emotionally distressing do you find this behaviour?

[ ] not at all

[ ] minimally

[ ] mildly

[ ] moderately

[ ] severely

[ ] very severely or extremely

Date of this examination

1 2 fam. day month year

Total Sleep (AxB)

Subject's initials

L. Appetite and Eating Disorders

Has he/she had any change in appetite, weight, or eating habits (count as NA if the patient is incapacitated and has to be fed)? Has there been any change in type of food he/she prefers?

not applicable [ ] no ([ ] proceed to next screening question) [ ] yes ([ ] proceed to subquestions)

Has he/she had a loss of appetite?

Has he/she had an increase in appetite?

Has he/she had a loss of weight?

Has he/she gained weight?

Has he/she had a change in eating behaviour such as putting too much food in his/her mouth at once?

Has he/she had a change in the kind of food he/she likes such as eating too many sweets or other specific types of food?

Has he/she developed eating behaviours such as eating exactly the same types of food each day or eating the food in exactly the same order?

Have there been any other changes in appetite or eating that I haven't asked about?

A-Frequency:

occasionally – less than once per week

often – about once per week

frequently – several times per week but less than every day

very frequently – once or more per day

B-Severity:

mild – changes in appetite or eating are present but have not led to changes in weight and are not disturbing

moderate – changes in appetite or eating are present and cause minor fluctuations in weight

marked – obvious changes in appetite or eating are present and cause fluctuations in weight, are embarrassing, or otherwise disturb the patient

C-Distress:

How emotionally distressing do you find this behaviour?

not at all

minimally

mildly

moderately

severely

very severely or extremely

Date of this examination

1 2 fam. day month year

Total Appetite and eating disorders (AxB)

Summary Score Sheet

Caregiver Distress

(A) Delusions .....

(B) Hallucinations .....

(C) Agitation/Aggression .....

(D) Depression/Dysphoria .....

(E) Anxiety .....

(F) Elation/Euphoria .....

(G) Apathy/Indifference .....

(H) Disinhibition .....

(I) Irritability/Lability .....

(J) Aberrant motor behaviour .....

(K) Sleep .....

(L) Appetite and eating disorders .....

Total

(maximum 144) (minimum 60)

Subject's initials:

Date of this examination:

1 2 fam. day month year

9.7. Brief Psychiatric Rating Scale

Introduce all questions with "During the past week have you..."

*1. SOMATIC CONCERN: Degree of concern over present bodily health. Rate the degree to which physical health is perceived as a problem by the patient, whether complaints have a realistic basis or not. Do not rate mere reporting of somatic symptoms. Rate only concern for (or worrying about) physical problems (real or imagined). Rate on the basis of reported (i.e., subjective) information pertaining to the past week.

1 = Not reported

2 = Very Mild: occasionally is somewhat concerned about body, symptoms, or physical illness

3 = Mild: occasionally is moderately concerned, or often is somewhat concerned

4 = Moderate: occasionally is very concerned, or often is moderately concerned

5 = Moderately Severe: often is very concerned

6 = Severe: is very concerned most of the time

7 = Very Severe: is very concerned nearly all of the time

9 = Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked evasiveness/guardedness; or Not assessed

*2. ANXIETY: Worry, fear, or overconcern for present or future. Rate solely on the basis of verbal report of patient's own subjective experiences pertaining to the past week. Do not infer anxiety from physical signs or from neurotic defense mechanisms. Do not rate if restricted to somatic concern.

1 = Not reported

2 = Very Mild: occasionally feels somewhat anxious

3 = Mild: occasionally feels moderately anxious, or often feels somewhat anxious

4 = Moderate: occasionally feels very anxious, or often feels moderately anxious

5 = Moderately Severe: often feels very anxious

6 = Severe: feels very anxious most of the time

7 = Very Severe: feels very anxious nearly all of the time

9 = Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked evasiveness/guardedness; or Not assessed

3. EMOTIONAL WITHDRAWAL: Deficiency in relating to the interviewer and to the interview situation. Overt manifestations of this deficiency include poor/absence of eye contact, failure to orient oneself physically toward the interviewer, and a general lack of involvement or engagement in the interview. Distinguish from BLUNTED AFFECT, in which deficits in facial expression, body gesture, and voice pattern are scored. Rate on the basis of observations made during the interview.

1 = Not observed

2 = Very Mild: e.g., occasionally exhibits poor eye contact

3 = Mild: e.g., as above, but more frequent

4 = Moderate: e.g., exhibits little eye contact, but still seems engaged in the interview and is appropriately responsive to all questions

5 = Moderately Severe: e.g., stares at floor or orients self away from interviewer, but still seems moderately engaged

6 = Severe: e.g., as above, but more persistent or pervasive

7 = Very Severe: e.g., appears "spacey" or "out of it" (total absence of emotional relatedness), and is disproportionately uninvolved or unengaged in the interview (DO NOT SCORE IF EXPLAINED BY DISORIENTATION.)

4. CONCEPTUAL DISORGANIZATION: Degree of speech incomprehensibility. Include any type of formal thought disorder (e.g., loose associations, incoherence, flight of ideas, neologisms). DO NOT include mere circumstantiality or pressured speech, even if marked. DO NOT rate on the basis of the patient's subjective impressions (e.g., "my thoughts are racing. I can't hold a thought," "my thinking gets all mixed up"). Rate ONLY on the basis of observations made during the interview.

1 = Not observed

2 = Very Mild: e.g., somewhat vague, but of doubtful clinical significance

3 = Mild: e.g., frequently vague, but the interview is able to progress smoothly; occasional loosening of associations

4 = Moderate: e.g., occasional irrelevant statements, infrequent use of neologisms, or moderate loosening of associations.

5 = Moderately Severe: as above, but more frequent

6 = Severe: formal thought disorder is present for most of the interview, and the interview is severely strained

7 = Very Severe: very little coherent information can be obtained

5. GUILT FEELINGS: Overconcern or remorse for past behavior. Rate on the basis of the patient's subjective experiences of guilt as evidenced by verbal report pertaining to the past week. Do not infer guilt feelings from depression, anxiety or neurotic defenses.

1 = Not reported

2 = Very Mild: occasionally feels somewhat guilty

3 = Mild: occasionally feels moderately guilty, or often feels somewhat guilty

4 = Moderate: occasionally feels very guilty, or often feels moderately guilty

5 = Moderately Severe: often feels very guilty

6 = Severe: feels very guilty most of the time, or encapsulated delusion of guilt

7 = Very Severe: agonizing constant feelings of guilt, or pervasive delusion(s) of guilt

9 = Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked evasiveness/guardedness; or Not assessed

6. TENSION: Rate motor restlessness (agitation) observed during the interview. DO NOT rate on the basis of subjective experiences reported by the patient. Disregard suspected pathogenesis (e.g., tardive dyskinesia).

1 = Not observed

2 = Very Mild: e.g., occasionally fidgets

3 = Mild: e.g., frequently fidgets

4 = Moderate: e.g., constantly fidgets, or frequently fidgets, wrings hands and pulls clothing

5 = Moderately Severe: e.g., constantly fidgets, wrings hands and pulls clothing

6 = Severe: e.g., cannot remain seated (i.e., must pace)

7 = Very Severe: e.g., paces in a frantic manner

7. MANNERISMS AND POSTURING: Unusual and unnatural motor behavior. Rate only abnormality of movements. Do not rate simple heightened motor activity here. Consider frequency, duration, and degree of bizarreness. Disregard suspected pathogenesis.

1 = Not observed

2 = Very Mild: odd behavior but of doubtful clinical significance, e.g., occasional unprompted smiling, infrequent lip movements

3 = Mild: strange behavior but not obviously bizarre, e.g., infrequent head-tilting (side to side) in a rhythmic fashion, intermittent abnormal finger movements

4 = Moderate: e.g., assumes unnatural position for a brief period of time, infrequent tongue protrusions, rocking, facial grimacing

5 = Moderately Severe: e.g., assumes and maintains unnatural position throughout interview, unusual movements in several body areas

6 = Severe: as above, but more frequent, intense, or pervasive

7 = Very Severe: e.g., bizarre posturing throughout most of the interview, continuous abnormal movements in several body areas

*8. GRANDIOSITY: Inflated self-esteem (self-confidence), or inflated appraisal of one's talents, powers, abilities, accomplishments, knowledge, importance, or identity. Do not score mere grandiose quality of claims (e.g., "I'm the worst sinner in the world," "The entire country is trying to kill me") unless the guilt/persecution is related to some special, exaggerated attributes of the individual. Also, the patient must claim exaggerated attributes: e.g., if patient denies talents, powers, etc., even if he or she states that others indicate that he/she has these attributes, this item should not be scored. Rate on the basis of reported (i.e., subjective) information pertaining to the past week.

1 = Not reported

2 = Very Mild: e.g., is more confident than most people, but of only possible clinical significance

3 = Mild: e.g., definitely inflated self-esteem or exaggerates talents somewhat out of proportion to the circumstances

4 = Moderate: e.g., inflated self-esteem clearly out of proportion to the circumstances, or suspected grandiose delusion(s)

5 = Moderately Severe: e.g., a single (definite) encapsulated grandiose delusion, or multiple (definite) encapsulated grandiose delusion, or multiple (definite) fragmentary grandiose delusions

6 = Severe: e.g., a single (definite) grandiose delusion/delusional system, or multiple (definite) grandiose delusions that the patient seems preoccupied with

7 = Very Severe: e.g., as above, but nearly all conversation is directed towards the patient's grandiose delusion(s)

9 = Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked evasiveness/guardedness; or Not assessed

*9. DEPRESSIVE MOOD: Subjective report of feeling depressed, blue, "down in the dumps," etc. Rate only degree of reported depression. Do not rate on the basis of inferences concerning depression based upon general retardation and somatic complaints. Rate on the basis of reported (i.e., subjective) information pertaining to the past week.

1 = Not reported

2 = Very Mild: occasionally feels somewhat depressed

3 = Mild: occasionally feels moderately depressed, or often feels somewhat depressed

4 = Moderate: occasionally feels very depressed, or often feels moderately depressed

5 = Moderately Severe: often feels very depressed

6 = Severe: feels very depressed most of the time

7 = Very Severe: feels very depressed nearly all of the time

9 = Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked evasiveness/guardedness; or Not assessed

*10. HOSTILITY: Animosity, contempt, belligerence, disdain for other people outside the interview situation. Rate solely on the basis of the verbal report of feelings and actions of the patient toward others during the past week. Do not infer hostility from neurotic defenses, anxiety or somatic complaints.

1 = Not reported

2 = Very Mild: occasionally feels somewhat angry

3 = Mild: often feels somewhat angry, or occasionally feels moderately angry

4 = Moderate: occasionally feels very angry, or often feels moderately angry

5 = Moderately Severe: often feels very angry

6 = Severe: has acted on his anger by becoming verbally or physically abusive on one or two occasions

7 = Very Severe: has acted on his anger on several occasions

9 = Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked evasiveness/guardedness; or Not assessed

*11. SUSPICIOUSNESS: Belief (delusional or otherwise) that others have now, or have had in the past, malicious or discriminatory intent toward the patient. On the basis of verbal report, rate only those suspicions which are currently held whether

they concern past or present circumstances. Rate on the basis of reported (i.e., subjective) information pertaining to the past week.

1 = Not reported

2 = Very Mild: rare instances of distrustfulness which may or may not be warranted by the situation

3 = Mild: occasional instances of suspiciousness that are definitely not warranted by the situation

4 = Moderate: more frequent suspiciousness, or transient ideas of reference

5 = Moderately Severe: pervasive suspiciousness, frequent ideas of reference, or an encapsulated delusion

6 = Severe: definite, delusion(s) of reference or persecution that is (are) not wholly pervasive (e.g., an encapsulated delusion)

7 = Very Severe: as above, but more widespread, frequent, or intense

9 = Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked evasiveness/guardedness; or Not assessed

*12. HALLUCINATORY BEHAVIOR: Perceptions (in any sensory modality) in the absence of an identifiable external stimulus. Rate only those experienced that have occurred during the last week. DO NOT rate "voices in my head," or "visions in my mind" unless the patient can differentiate between these experiences and his or her thoughts.

1 = Not reported

2 = Very Mild: suspected hallucinations only

3 = Mild: definite hallucinations, but insignificant, infrequent, or transient (e.g., occasional formless visual hallucinations, a voice calling the patient's name)

4 = Moderate: as above, but more frequent or extensive (e.g., frequently sees the devil's face, two voices carry on lengthy conversations)

5 = Moderately Severe: hallucinations are experienced nearly every day, or are a source of extreme distress

6 = Severe: as above, and has had a moderate impact on the patient's behavior (e.g., concentration difficulties leading to impaired work functioning)

7 = Very Severe: as above, and has had a severe impact (e.g., attempts suicide in response to command hallucinations)

9 = Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked evasiveness/guardedness; or Not assessed

13. MOTOR RETARDATION: Reduction in energy level evidenced in slowed movements. Rate on the basis of observed behavior of the patient only. Do not rate on the basis of the patient's subjective impression of his or her own energy level.

1 = Not observed

2 = Very Mild and of doubtful clinical significance

3 = Mild: e.g., conversation is somewhat retarded, movements somewhat slowed

4 = Moderate: e.g., conversation is noticeably retarded but not strained

5 = Moderately Severe: e.g., conversation is strained, moves very slowly

6 = Severe: e.g., conversation is difficult to maintain, hardly moves at all

7 = Very Severe: e.g., conversation is almost impossible, does not move at all throughout the interview

14. UNCOOPERATIVENESS: Evidence of resistance, unfriendliness, resentment, and lack of readiness to cooperate with the interviewer. Rate only on the basis of the

patient's attitude and responses to the interviewer and the interview situation. Do not rate on the basis of reported resentment or uncooperativeness outside the interview situation.

1 = Not observed

2 = Very Mild: e.g., does not seem motivated

3 = Mild: e.g., seems evasive in certain areas

4 = Moderate: e.g., monosyllabic, fails to elaborate spontaneously, somewhat unfriendly

5 = Moderately Severe: e.g., expresses resentment and is unfriendly throughout the interview

6 = Severe: e.g., refuses to answer a number of questions

7 = Very Severe: e.g., refuses to answer most questions

15. UNUSUAL THOUGHT CONTENT: Severity of delusions of any type—consider conviction, and effect on actions. Assume full conviction if patient has acted on his or her beliefs. Rate on the basis of reported (i.e., subjective) information pertaining to past week.

1 = Not reported

2 = Very Mild: delusion(s) suspected or likely

3 = Mild: at times, patient questions his or her belief(s) (partial delusion)

4 = Moderate: full delusional conviction, but delusion(s) has little or no influence on behavior

5 = Moderately Severe: full delusional conviction, but delusion(s) has only occasional impact on behavior

6 = Severe: delusion(s) has significant effect, e.g., neglects responsibilities because of preoccupation with belief that he/she is God

7 = Very Severe: delusion(s) has major impact, e.g., stops eating because believes food is poisoned

9 = Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked evasiveness/guardedness; or Not assessed

16. BLUNTED AFFECT: Diminished affective responsivity, as characterized by deficits in facial expression, body gesture, and voice pattern. Distinguish from EMOTIONAL WITHDRAWAL, in which the focus is on interpersonal impairment rather than affect. Consider degree and consistency of impairment. Rate based on observations made during interview.

1 = Not observed

2 = Very Mild: e.g., occasionally seems indifferent to material that is usually accompanied by some show of emotion

3 = Mild: e.g., somewhat diminished facial expression, or somewhat monotonous voice or somewhat restricted gestures

4 = Moderate: e.g., as above, but more intense, prolonged, or frequent

5 = Moderately Severe: e.g., flattening of affect, including at least two of the three features: severe lack of facial expression, monotonous voice, or restricted body gestures

6 = Severe: e.g., profound flattening of affect

7 = Very Severe: e.g., totally monotonous voice, and total lack of expressive gestures throughout the evaluation

17. EXCITEMENT: Heightened emotional tone, including irritability and expansiveness (hypomanic affect). Do not infer affect from statements of grandiose delusions. Rate based on observations made during interview.

1 = Not observed

2 = Very Mild and of doubtful clinical significance

3 = Mild: e.g., irritable or expansive at times

4 = Moderate: e.g., frequently irritable or expansive

5 = Moderately Severe: e.g., constantly irritable or expansive; or, at times, enraged or euphoric

6 = Severe: e.g., enraged or euphoric throughout most of the interview.

7 = Very Severe: e.g., as above, but to such a degree that the interview must be terminated prematurely

18. DISORIENTATION: Confusion or lack of proper association for person, place or time. Rate based on observations made during interview.

1 = Not observed

2 = Very Mild: e.g., seems somewhat confused

3 = Mild: e.g., indicated 1982 when, in fact, it is 1983

4 = Moderate: e.g., indicates 1978

5 = Moderately Severe: e.g., is unsure where he/she is

6 = Severe: e.g., has no idea where he/she is

7 = Very Severe: e.g., does not know who he/she is

9 = Cannot be assessed adequately because of severe formal thought disorder, uncooperativeness, or marked evasiveness/guardedness; or Not assessed

19. SEVERITY OF ILLNESS: Considering your total clinical experience with this patient population, how mentally ill is the patient at this time?

1 = Normal, not at all ill

2 = Borderline mentally ill

3 = Mildly ill

4 = Moderately ill

5 = Markedly ill

6 = Severely ill

7 = Among the most severely ill patients

20. GLOBAL IMPROVEMENT: Rate total improvement whether or not, in your judgment, it is due to treatment.

At baseline assessment, mark "Not assessed" for item 20.

For assessments up to the start of double-blind medication, rate Global Improvement compared to baseline. For assessments following the start of double-blind medication, rate Global Improvement compared to the start of double-blind.

1 = Very much improved

2 = Much improved

3 = Minimally improved

4 = No change

5 = Minimally worse

6 = Much worse

7 = Very much worse

9 = Not assessed

*Ratings based primarily upon verbal report.

9.8. LETTERS & INFORMATION SHEETS (SUBJECTS & CONTROLS)

INFORMATION SHEET (SUBJECTS)

People who suffer from seizures (fits) often suffer from emotional problems like anxiety and depression that affect their lives. We are developing some simple questionnaires that would help your doctor identify these problems. We would like to see you and to have you reply to some questions, as this will help us in our research.

The assessment will begin with some questionnaires that we will send to you in the post. These will take about 40 minutes on average to complete. A Research Assistant will then meet with you to ask you some questions, in person and on a computer. This meeting could take place in your doctors' surgery, or in the comfort of your own home, as is your preference. This too should take no longer than 40 minutes.

Depending on the results of these assessments, you may be contacted by the epilepsy specialist nurse from your doctor's surgery, and offered a consultation with a specialist team. This too could take place in the comfort of your home, or in the surgery, as is your preference.

With your permission we would also like to talk to a close relative, friend or carer, nominated by you, who knows you well. This would be to collect information about how the illness may have affected you as a person. This could be done over the

telephone, or in person, depending on your preference. They would also be requested to reply to a questionnaire.

The decision whether to take part is entirely yours. Whatever you decide, it will not affect the medical care that you receive now or in the future. You could refuse to take part in any aspect of the study, and could withdraw consent at any time without giving reasons. The results of this examination will be summarised in a letter to your doctor, as this could help him/her make decisions about your treatment.

Information that you give us will be treated confidentially (like any medical notes). You will be identified only by a code, and not by your name. Data will be stored in computers and code protected. Scientific findings that are published will not identify individual participants in any way.

If you have any queries please do not hesitate to get in touch with us and we will be happy to answer them. We hope you will find it possible o help us in our research.

Letter to the subject with epilepsy (On Surgery Letterhead):

Dear ------

Doctors from the Institute of Neurology and National Hospital for Neurology and Neurosurgery are working with us on a research project, about the emotional aspects of epilepsy. They would like to meet with you, and to ask you some questions in this regard. This could be done in the comfort of your home, if that is your preference. Alternately, we would be happy to arrange and pay for a taxi that will bring you to the surgery and take you home, if that is more convenient to you. Our epilepsy clinical nurse specialist, will introduce you to the concerned doctors, and help in clarifying any doubts you may have. I enclose an information sheet about the project, and look forward to your co-operation and support.

Signed

GP Principal/ Consultant

Research Fellow

INFORMATION SHEET (CONTROLS)

People who suffer from seizures (fits) often suffer from emotional problems like anxiety and depression that affect their lives. We are developing some simple questionnaires that would help your doctor identify these problems. To do this effectively we need to compare their answers with those of people who do not suffer with epilepsy. We would like to see you and to have you reply to some questions, as this will help us in our research.

The assessment will consist of two short questionnaires, each of which would take no more than 10 minutes on average to complete. You will also be asked to reply to a questionnaire on the computer, and this should take no more than 20 minutes. This could be done either in your doctor's surgery, by appointment, or in the convenience of your own home, depending on your preference.

The decision about taking part is left to you. Whatever you decide, it will not affect the medical care that you receive, now or in the future. You could refuse to take part in the study or withdraw consent at any time without giving reasons.
Information that you give us will be treated confidentially (like any medical notes).

You will be identified only by a code, and not by your name. Data will be stored in computers and code protected. Scientific findings that are published will not identify individual participants in any way. The results of this examination will be discussed with you, and summarised in a letter to your doctor.

If you have any queries please do not hesitate to get in touch with us and we will be happy to answer them. We hope you will find it possible to help us in our research.

Letter to Control subjects (On Surgery Letterhead):

Dear------

Doctors from the Institute of Neurology and National Hospital for Neurology and Neurosurgery are working with us on a research project, about the emotional aspects of epilepsy. They need to compare people who suffer from epilepsy (seizures/fits) with others like you, who do not suffer from this condition. You have been randomly selected from our practise register, and are being approached for this purpose.

We would like to meet with you, and to ask you some questions. This could be done in the comfort of your home, if that is your preference. Alternately, we would be happy to arrange and pay for a taxi that will bring you to the surgery and take you back home, if that is more convenient to you. Our nurse specialist, will introduce you to the concerned doctors, and help in clarifying any doubts you may have. I enclose an information sheet about the project, and look forward to your co-operation and support.

Signed

GP Principal/Consultant Research Fellow